1-1-2022

Association between recent overdose and chronic pain among individuals in treatment for opioid use disorder

Sarah M. Hartz

Robert C. Culverhouse

Carrie M. Mintz

Matthew S. Ellis

Zachary A. Kasper

See next page for additional authors

Authors

Sarah M. Hartz, Robert C. Culverhouse, Carrie M. Mintz, Matthew S. Ellis, Zachary A. Kasper, Patricia Cavazos-Rehg, Richard A. Grucza, Laura J. Bierut, and Theodore J. Cicero

Association between recent overdose and chronic pain among individuals in treatment for opioid use disorder

Sarah M. Hartz[1]*, Robert C. Culverhouse[2], Carrie M. Mintz[1], Matthew S. Ellis[1], Zachary A. Kasper[1], Patricia Cavazos-Rehg[1], Richard A. Grucza[3], Laura J. Bierut[1], Theodore J. Cicero[1]

1 Department of Psychiatry, Washington University School of Medicine in St. Louis, St. Louis, Missouri, United States of America, 2 Department of Medicine and Division of Biostatistics, Washington University School of Medicine in St. Louis, St. Louis, Missouri, United States of America, 3 Department of Family & Community Medicine, St. Louis University School of Medicine, St. Louis, Missouri, United States of America

* hartzs@wustl.edu

Abstract

Chronic pain increases risk for opioid overdose among individuals with opioid use disorder. The purpose of this study is to evaluate the relationship between recent overdose and whether or not chronic pain is active. 3,577 individuals in treatment for opioid use disorder in 2017 or 2018 were surveyed regarding recent overdoses and chronic pain. Demographics from the 2017 Treatment Episode Data Set, which includes all U.S. facilities licensed or certified to provide substance use care, were used to evaluate the generalizability of the sample. χ^2 tests and logistic regression models were used to compare associations between recent overdoses and chronic pain. Specifically, active chronic pain was associated with opioid overdose among people in treatment for opioid use disorder. Individuals with active chronic pain were more likely to have had a past month opioid overdose than those with no history chronic pain (adjusted OR = 1.55, 95% CI 1.16–2.08, p = 0.0003). In contrast, individuals with prior chronic pain, but no symptoms in the past 30 days, had a risk of past month opioid overdose similar to those with no history of chronic pain (adjusted OR = 0.88, 95% CI 0.66–1.17, p = 0.38). This suggests that the incorporation of treatment for chronic pain into treatment for opioid use disorder may reduce opioid overdoses.

Introduction

The opioid overdose crisis continues to ravage the United States: deaths due to opioid overdose surpassed motor vehicle accidents as a leading cause of death in 2016 [1], and had a record high in the 12-month period ending in April 2021 [2]. The initial increase in opioid overdose was partially fueled by availability and misuse of opioids prescribed for pain [3, 4], progressed to an increase in heroin use [5] and most recently has transitioned to a surge in use of potent synthetic opioids, primarily illicitly manufactured fentanyl.

Chronic pain contributes to both non-fatal and fatal overdoses: chronic pain is associated with a lifetime history of non-fatal overdose [6, 7] and post-mortem interviews with friends

and family members suggest that pain was a contributing factor for a large proportion of fatal opioid overdoses [8]. In addition, lack of treatment of chronic pain is the primary reason for relapse after seeking treatment for opioid use disorder (OUD) [9], and higher pain levels in the year prior to treatment for substance use disorder are associated with 1.26 higher odds of overdose in the year following treatment [10]. Despite this, the current standard of care for treatment of OUD does not involve evaluation and treatment of chronic pain [11].

Epidemiological studies of chronic pain suggest it has a fluctuating course with acute exacerbations (or flare-ups) and periods of relatively few or no symptoms [12–16]. There are multiple trajectories and patterns to chronic pain [17, 18]. Most commonly, individuals have multiple episodes of pain separated by asymptomatic periods or periods of lesser severity [19, 20]. Evidence suggests that active chronic pain in individuals with OUD is complicated by increased pain sensitivity that continues during opioid maintenance therapy [21]. Although the natural assumption would be that active chronic pain is directly associated with opioid overdose, to our knowledge, prior evaluation of this hypothesis does not exist. Specifically, no study has evaluated the relationship between overdose and active chronic pain among individuals in treatment for OUD. Determining that active chronic pain increases risk for opioid overdose more than prior history alone would provide a strong argument to include treatment for chronic pain in standard treatment for OUD.

Using a dataset of individuals in treatment for OUD, we divided the sample into three groups:"active chronic pain" defined as chronic pain within the past 30 days, "prior history of chronic pain" defined as past chronic pain without pain in the past 30 days, and those who never had chronic pain. To test the hypothesis that active chronic pain is a specific risk factor for overdose in OUD, we evaluated the association between opioid overdose in the month prior to treatment and chronic pain status in a large cross-sectional sample of individuals in treatment for OUD.

Materials and methods

Data

This study analyzed data from the Survey of Key Informants' Patients (SKIP) Program. SKIP, an ongoing collection of over 24,000 individuals recruited from 154 treatment centers nationwide (including both residential and outpatient treatment), collects data on non-medical prescription opioid use and other illicit drug use [3, 22–28]. SKIP was started in 2008 and is updated quarterly to enable rapid identification of changes in patterns of opioid use. Patients newly enrolled at participating treatment centers complete an anonymous questionnaire about their primary drug of abuse, sources of drug acquisition, drug use in the month prior to treatment, and routes of use as well as other assessments of mental health and psychiatric disorders. SKIP is a component of The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS ®) System (https://www.radars.org/), a mosaic of programs to monitor drug misuse and abuse and has been validated against other RADARS opioid surveillance programs [5, 29].

We analyzed SKIP questionnaires completed by adults aged 18 to 83 entering treatment for OUD in 2017 and 2018. Participants were from all regions of the continental US, Alaska and Washington DC. The overall response rate of the SKIP questionnaire was 87%, resulting in an analyzable sample of N = 3,577 individuals which we will refer to as the SKIP data.

This study was approved by the Institutional Review Board at Washington University in St. Louis School of Medicine. Risks of the study were explained on the first page of the SKIP questionnaire and return of the survey was considered informed written consent. No Health Insurance Portability and Accountability Act (HIPAA) identifiers were collected.

Variable definitions

Individuals were classified into three opioid overdose categories: past-month opioid overdose, earlier opioid overdose (i.e., individuals who have an opioid overdose, but not in the past month), and no past opioid overdose. History of opioid overdose was defined based on answers to the following question:

Have you sought medical treatment for:

    a. Heroin overdose [select one: never, past month, longer ago]

    b. Prescription opioid overdose [select one: never, past month, longer ago]

Individuals were defined as having an opioid overdose in the past month if they answered "past month" to either (a) or (b). Of those who did not report a past month overdose, individuals were defined as having a prior overdose if they answered "longer ago" to either (a) or (b). The remaining individuals who answered at least one of the two questions were defined as having no prior opioid overdose.

Chronic pain was queried using the following question:

For the following questions, chronic pain refers to pain that has lasted for at least 3 months. This pain can either occur constantly or flare up frequently. Have you suffered from chronic pain?

[No, Yes in the last 7 days, Yes in the last 30 days, Yes in the last 12 months, Yes in my lifetime]

Based on patterns of symptomatic and asymptomatic periods of chronic pain, active chronic pain was defined by answering "Yes, in the last 7 days" or "Yes, in the last 30 days". Prior history of chronic pain was defined as answering "Yes in the last 12 months" or "Yes in my lifetime", without meeting criteria for active chronic pain [20].

Race and ethnicity in SKIP were categorized as non-Hispanic Caucasian, non-Hispanic African American, Hispanic, American Indian or Alaskan native, or Other race based on answers to the question "What best describes your race/ethnicity?". Gender was defined as "Female" or "Male" as responses to the question "What is your gender?"

Because one of the strongest risk factors for substance use disorder is early-onset substance use, we constructed an early-onset substance use variable defined as having used any of the following substances by age 16: prescription opioids, heroin, methamphetamines, crack/cocaine, ecstasy, or hallucinogens. Participants were asked to select formulations of substances that they had used in the past month to get high, and the methods with which they used them (swallowed whole, dissolved in mouth, chewed, smoked, snorted and/or intravenous). IV drug use in the past month was determined by selecting "intravenous" to any of the listed substances (buprenorphine, fentanyl, gabapentin, heroin, hydrocodone, hydromorphone, ketamine, loperamide, methadone, morphine, oxycodone, oxymorphone, pregabalin, sufentanil, tapentadol, tramadol, and THC/cannabanoid manufactured by pharmaceutical company). Current inpatient treatment was defined by selecting 'Inpatient' in response to "What kind(s) of treatment are you receiving".

We used early-onset substance use, gender, age, race and ethnicity, employment status (employed versus unemployed), and educational attainment (up to and including high school degree versus beyond high school degree) as covariates in our analyses.

Comparison to representative sample

SKIP participants were recruited from treatment centers throughout the continental US, but the treatment centers were not randomly selected. As a consequence, it is not known how

representative SKIP survey participants are of the OUD treatment population. To better understand this, we compared the available demographics from for individuals with a primary substance of heroin or other opioid use in the 2017 Treatment Episode Data Set (TEDS), a comprehensive dataset of admissions to substance use disorder treatment facilities in the US, to the same demographics in SKIP. The demographic factors evaluated were gender, mean age, proportion of African American, proportion of European American, proportion of other ancestry, proportion with education beyond high school. Chi-square tests of independence [30] were used to determine whether the demographic factors differed between the two samples.

Statistical association analysis of the SKIP data

Our primary outcome was history of opioid overdose, as defined above, comparing individuals with an opioid overdose in the past month, individuals who had an opioid overdose >1 month ago, and individuals who never had an opioid overdose. First, we evaluated whether factors (gender, dichotomized age, education level, chronic pain status, etc.) were distributed non-uniformly across the three groups using χ^2 tests. (i.e. whether any of these factors had a statistically significant association with opioid overdose). Next, logistic regression was used to calculate the association between past month overdose and chronic pain status. Analyses were run with chronic pain status alone, chronic pain status plus sociodemographic factors (gender, age, race and ethnicity, employment status, educational attainment, and use of illicit substances at or before age 16), and chronic pain status plus factors related to OUD severity (past month heroin or fentanyl use, past month intravenous (IV) drug use, and inpatient treatment). All statistical analyses were performed using SAS 9.4 [31].

Missing data

Of the over 24,000 individuals in the SKIP study, N = 3,738 completed the substance use survey. Of these 161 (4%) were missing information regarding either opioid overdose or chronic pain and were excluded from all analyses, for a primary sample size of 3,577. N = 32 (0.9%) did not include gender, N = 63 (2%) did not include employment status, and N = 303 (8%) did not include information regarding inpatient or outpatient treatment. Missing data were dropped when those variables were included in analyses.

Results

SKIP data were divided into three mutually exclusive groups of individuals: those who overdosed on opioids in the past month (N = 341, 10%), those who overdosed on opioids prior to the past month (N = 1,090, 30%), and those who had never overdosed on opioids (N = 2,146, 60%). We then evaluated whether any demographic factors were distributed differentially across the opioid overdose categories (Table 1). Gender was strongly associated with overdose (p<0.0001); men in treatment for OUD more likely to have either a past month overdose or a prior overdose (10% and 33%, respectively) compared to women in treatment for OUD (8% and 26%, respectively). Younger individuals in treatment for OUD (age 30 or less) were more likely to have had a recent overdose than older individuals (11% vs 8%, respectively, p = 0.02). Differences in patterns of overdose were also seen by self-defined race and ethnicity (Table 1, p<0.0001). Non-Hispanic African Americans in treatment for OUD had the highest past month overdose (13%) followed by non-Hispanic Caucasians (9%). Native Americans in treatment for OUD had the lowest rate of past month overdoses (5%). High school degree, health insurance status, and employment status did not have an association with overdose (p>0.05).

Table 1. Distributions and associations of past-month overdose with sociodemographic factors among N = 3,577 people in treatment for opioid use disorder.

	Past month OD N = 341	Earlier OD N = 1,090	Never OD N = 2,146	χ^2 p-value
	10%	30%	60%	
Gender[+]				<0.0001
Female (N = 2,180)	8%	26%	66%	
Male (N = 1,365)	10%	33%	56%	
Age				0.02
<30 (N = 1,276)	11%	30%	59%	
> = 30 (N = 2,301)	8%	31%	61%	
Race & Ethnicity				<0.0001
African American, non-Hispanic (N = 452)	13%	22%	65%	
Caucasian, non-Hispanic (N = 2,614)	9%	33%	57%	
Hispanic (N = 200)	8%	25%	67%	
Native American (N = 151)	5%	13%	82%	
Other race (N = 160)	8%	30%	61%	
Education				0.05
Up to and including High School degree (N = 2,084)	9%	32%	59%	
Beyond High School degree (N = 1,493)	10%	28%	62%	
Health Insurance				0.75
Uninsured (N = 1,162)	10%	30%	60%	
Insured (N = 2,415)	9%	31%	60%	
Employment[+]				0.15
Unemployed (N = 1,974)	10%	31%	59%	
Employed (N = 1,540)	9%	29%	62%	
Used illicit substances by age 16 (not including marijuana)				<0.0001
No (N = 1,991)	8%	25%	67%	
Yes (N = 1,586)	11%	38%	52%	

OD = overdose

[+]Missing in some participants

Individuals who started using illicit substances by age 16 (excluding marijuana) had higher rates of both past month overdose (11% vs. 8%) and earlier overdose (38% vs. 25%, p<0.0001).

To evaluate the representativeness of our sample, we examined the demographic alignment of the SKIP data, our sample of N = 3,577 individual survey respondents in treatment for OUD in 2017 and 2018, with the N = 645,285 treatment admissions in 2017 for OUD registered in the national database TEDS (Table 2). Overall, the two samples look similar demographically with respect to the categorizations as presented in the table. The dichotomous distributions of gender and age did not statistically differ between TEDS and SKIP. Because race and ethnicity were separated in TEDS and combined in SKIP, we were unable to statistically test the distributions between the two groups. It appears the proportions of African Americans (14% in TEDS vs 13% in SKIP) and Caucasians (73% in both data sets) are similar in the two samples, but that SKIP is oversampled for Native Americans & Pacific Islanders and undersampled for Hispanics. If the race and ethnicity groups in SKIP were collapsed to African Americans, Caucasians, and other/unknown (13% in TEDS vs 15% in SKIP), the Chi-Square p-value for the difference between SKIP and TEDS is 0.17. The demographic factor that differs significantly between the two samples is educational attainment: 31% of the TEDS sample had

Table 2. Demographic comparison of individuals in treatment for opioid use disorder from the Treatment Episode Data Set (TEDS), a national database from treatment admissions and discharges at facilities that are licensed or certified by a state substance abuse agency, and the Survey of Key Informants' Patients (SKIP), an in-depth survey of individuals from selected treatment centers nationwide. The p-value is based on the chi-square test for homogeneity.

	TEDS	SKIP data	p-value
N	645,285	3,577	
Year(s)	2017	2017–2018	
Gender			0.51
Male	61.2%	61.3%	
Female	38.8%	38.7%	
Age			0.56
≤ 30 years old	39.4%	39.5%	
>30 years old	60.6%	60.5%	
Race			
African American or Black	13.7%		
Caucasian	73.1%		
Native American or Pacific Islander	1.9%		
Other or unknown race	11.0%		
Ethnicity			
Hispanic or Latino	11.7%		
Non-Hispanic or Latino	88.3%		
Combined Race & Ethnicity			
African American		12.6%	
Caucasian		72.9%	
Hispanic		5.6%	
Native American or Pacific Islander		4.2%	
Other or unknown race		4.7%	
Education			<0.001
High school degree or less	69.0%	64.3%	
Beyond high school degree	31.0%	35.7%	

https://doi.org/10.1371/journal.pone.0271379.t002

schooling beyond a high school degree relative to 36% of the SKIP sample (p<0.001). Of note, TEDS measured years of education, whereas SKIP measured terminal degree (with one option being "some college").

We then looked at the association of the opioid overdose groups with chronic pain and with other factors related to severity of substance use disorder including past month use of heroin or fentanyl, past month use of IV drugs, and inpatient treatment (Table 3). Each of these factors was strongly associated with the overdose groups (p<0.0001).

To gain a clearer understanding of the association between chronic pain status and past month opioid overdose, we adjusted for the potential confounding factors (Table 4). Individuals with active chronic pain were more likely to have had a past month opioid overdose relative to both those who have never had chronic pain (sociodemographic and severity adjusted OR = 1.55, 95% CI 1.16–2.08, p = 0.003) and those with prior chronic pain (sociodemographic and severity adjusted OR = 1.77, 95% CI 1.30–2.42, p = <0.001). In contrast, the rate of past month opioid overdose in individuals with prior chronic pain was similar to the rate in individuals with no history of chronic pain (sociodemographic and severity adjusted OR = 0.88, 95% CI 0.66–1.17, p = 0.38). These associations were substantively unchanged regardless of the covariates included in the regression model.

Table 3. Distributions of past-month overdose with factors related to severity of opioid use disorder among N = 3,577 people in treatment for opioid use disorder.

	Past month OD N = 341	Earlier OD N = 1,090	Never OD N = 2,146	χ² p-value
	10%	**30%**	**60%**	
Chronic Pain				<0.0001
Never (N = 1,586)	9%	27%	64%	
Prior history (N = 1,213)	8%	36%	57%	
Active (N = 778)	13%	30%	57%	
Past month use of heroin or fentanyl				<0.0001
No (N = 2,634)	8%	27%	65%	
Yes (N = 943)	13%	39%	48%	
IV drugs in past month				<0.0001
No (N = 1,976)	5%	22%	73%	
Yes (N = 1,601)	14%	41%	44%	
Current inpatient treatment[+]				<0.0001
No (N = 1,563)	7%	29%	64%	
Yes (N = 1,711)	13%	33%	54%	

OD = overdose

[+]Missing in some participants

https://doi.org/10.1371/journal.pone.0271379.t003

Discussion

In a large-scale, nationwide study of individuals in treatment for OUD, we examined the association between active chronic pain and recent opioid overdose. We found that among those in treatment for OUD, men, younger individuals, non-Hispanic African Americans, and individuals who started using illicit substances by age 16 were more likely to have past month overdose. Active chronic pain was associated with increased rate of recent opioid overdose, whereas a history of prior chronic pain or no history of any chronic pain had similar rates of recent opioid overdose. In the SKIP sample of individuals in treatment for OUD, over 20% had active chronic pain and could potentially benefit from treatment of the pain, which is not currently the standard of care for treatment of OUD. To our knowledge, this study represents the first analysis of the association between active chronic pain and recent opioid overdose.

Table 4. Association between chronic pain status and past month overdose with different covariates in the model.
Individuals with past-month opioid overdose are compared to the remainder of the sample.

	Association with past month opioid overdose					
	No model covariates		Model includes sociodemographics[a]		Model includes sociodemographics[a] and SUD severity[b]	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Chronic Pain						
Never	reference		reference		reference	
Prior history	0.84 (0.64–1.10)	0.21	0.93 (0.71–1.24)	0.63	0.88 (0.66–1.17)	0.38
Active	1.53 (1.17–2.00)	0.02	1.62 (1.23–2.14)	0.0007	1.55 (1.16–2.08)	0.003

[a]gender, age, race, education, health insurance, employment, used illicit substances at or before age 16

[b]past month use of heroin or fentanyl, IV drug use in past month, current inpatient treatment

OR = odds ratio

CI = confidence interval

SUD = substance use disorder

https://doi.org/10.1371/journal.pone.0271379.t004

The need to treat pain in individuals with OUD has been highlighted by many studies [32–38]. There is some evidence that cognitive behavioral therapy is helpful for treatment of pain in OUD [39, 40]. Similarly, non-pharmacological treatment of active chronic pain has been associated with fewer opioid-related adverse outcomes in veterans [41]. There is also evidence showing that the combination of approaches including physical therapy, emotional and spiritual support, cognitive behavioral therapy, and non-opioid pharmacotherapies can reduce pain severity and improve functioning in those with chronic pain, preventing the onset of opioid misuse and OUD [42]. However, there remains a strong need for improved understanding of best practices for how to treat pain among individuals who have OUD [43, 44] and to ensure that quality pain management in OUD care is prioritized [9]. This is specifically relevant in light of the diversity of settings for treatment of OUD, where pain management experts are typically not integrated into the care team for treatment of substance use disorder.

Association between pain and overdose does not imply causality. Indeed, permanent neurophysiological changes in opioid receptor functionality may result from prolonged opioid use [21], which may make those with OUD more prone to chronic pain. Regardless of the etiology of the association between pain and overdose, a focus on non-pharmacologic management of chronic pain as a standard component in the treatment of OUD may be beneficial. The combination of the severity of the opioid overdose epidemic [45, 46] and the low risk of both non-opioid pharmacological therapy for chronic pain and non-pharmacological treatment of chronic pain suggests that the benefits of implementation of these therapies in the treatment of OUD would far outweigh the costs.

There are several limitations of this study. SKIP, although large, was recruited as a sample of convenience, potentially limiting the generalizability of the results. However these limitations are attenuated because the demographics of SKIP resemble the demographics of those with OUD in TEDS, the only national sample of individuals in treatment for substance use disorder. Unfortunately, TEDS does not track pain or other factors related to disease severity. To maximize generalizability, our findings are adjusted for demographic and illness-related factors. Another limitation is that the survey item used to determine opioid overdose asked about seeking medical treatment for overdose, rather than asking directly about recent overdose, and only includes non-fatal overdoses. Because of this, our sample is missing those who overdosed but did not seek medical treatment, and those who died from overdose. If people with prior chronic pain are more likely to have a fatal overdose, the interpretation of these results would change. Another limitation is that the SKIP data are cross sectional, and we are assuming that participants who reported both having chronic pain in the past month and an overdose in the past month overdosed while in chronic pain.

Further study is needed to clarify the observed association between active chronic pain and opioid overdose. Because only basic information regarding chronic pain was collected, an explicit evaluation of the history and treatment of chronic pain among individuals in treatment for OUD would help specify treatment recommendations. Similarly, more information about treatment for OUD which is not assessed in the SKIP survey such as history of treatment type and duration as well as method of administration would better inform the interpretation of the association between chronic pain and OUD.

Conclusions

Our findings have important ramifications for the treatment of OUD. The current standard of care for treatment of OUD neither includes an evaluation of pain, nor incorporates pain management [11]. Among people in treatment for OUD, we found that active chronic pain is highly prevalent, and rate of overdose among those with active chronic pain is much higher

than the rate of overdose both in those with prior chronic pain and in those who have never had chronic pain. Therefore, evaluation and management of active chronic pain in this high-risk population may be a step towards reducing overdose deaths.

Acknowledgments

Author Contributions

Conceptualization: Sarah M. Hartz, Matthew S. Ellis, Richard A. Grucza, Laura J. Bierut, Theodore J. Cicero.

Data curation: Matthew S. Ellis, Zachary A. Kasper, Theodore J. Cicero.

Formal analysis: Sarah M. Hartz, Matthew S. Ellis, Zachary A. Kasper.

Funding acquisition: Sarah M. Hartz.

Methodology: Sarah M. Hartz, Robert C. Culverhouse, Carrie M. Mintz, Matthew S. Ellis, Patricia Cavazos-Rehg, Richard A. Grucza, Laura J. Bierut, Theodore J. Cicero.

Supervision: Sarah M. Hartz.

Writing – original draft: Sarah M. Hartz, Robert C. Culverhouse, Carrie M. Mintz, Matthew S. Ellis, Zachary A. Kasper, Patricia Cavazos-Rehg, Richard A. Grucza, Laura J. Bierut, Theodore J. Cicero.

Writing – review & editing: Sarah M. Hartz, Robert C. Culverhouse, Carrie M. Mintz, Matthew S. Ellis, Zachary A. Kasper, Patricia Cavazos-Rehg, Richard A. Grucza, Laura J. Bierut, Theodore J. Cicero.

References

1. National Safety Council. Odds of Dying–Data Details 2022 [Available from: https://injuryfacts.nsc.org/all-injuries/preventable-death-overview/odds-of-dying/data-details/.

2. National Center for Health Statistics. Provisional Drug Overdose Death Counts 2021 [Available from: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

3. Cicero TJ, Ellis MS, Harney J. Shifting Patterns of Prescription Opioid and Heroin Abuse in the United States. The New England journal of medicine. 2015; 373(18):1789–90. https://doi.org/10.1056/NEJMc1505541 PMID: 26510045

4. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA psychiatry. 2014; 71(7):821–6. https://doi.org/10.1001/jamapsychiatry.2014.366 PMID: 24871348

5. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, et al. Trends in opioid analgesic abuse and mortality in the United States. The New England journal of medicine. 2015; 372 (3):241–8. https://doi.org/10.1056/NEJMsa1406143 PMID: 25587948

6. Bonar EE, Ilgen MA, Walton M, Bohnert AS. Associations among pain, non-medical prescription opioid use, and drug overdose history. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2014; 23(1):41–7.

7. Fernandez AC, Bush C, Bonar EE, Blow FC, Walton MA, Bohnert ASB. Alcohol and Drug Overdose and the Influence of Pain Conditions in an Addiction Treatment Sample. Journal of addiction medicine. 2019; 13(1):61–8. https://doi.org/10.1097/ADM.0000000000000451 PMID: 30161038

8. Yarborough BJ, Stumbo SP, Janoff SL, Yarborough MT, McCarty D, Chilcoat HD, et al. Understanding opioid overdose characteristics involving prescription and illicit opioids: A mixed methods analysis. Drug and alcohol dependence. 2016; 167:49–56. https://doi.org/10.1016/j.drugalcdep.2016.07.024 PMID: 27520885

9. Ellis MS, Kasper Z, Cicero T. Assessment of Chronic Pain Management in the Treatment of Opioid Use Disorder: Gaps in Care and Implications for Treatment Outcomes. The journal of pain: official journal of the American Pain Society. 2021; 22(4):432–9. https://doi.org/10.1016/j.jpain.2020.10.005 PMID: 33197581

10. Britton PC, Wines JD Jr., Conner KR. Non-fatal overdose in the 12 months following treatment for substance use disorders. Drug and alcohol dependence. 2010; 107(1):51–5. https://doi.org/10.1016/j.drugalcdep.2009.09.005 PMID: 19828263

11. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Journal of addiction medicine. 2015; 9(5):358–67. https://doi.org/10.1097/ADM.0000000000000166 PMID: 26406300

12. Croft P, Blyth FM, Windt Dvd. Chronic Pain Epidemiology: From Aetiology to Public Health. New York: Oxford University Press; 2010.

13. Von Korff M. Studying the natural history of back pain. Spine (Phila Pa 1976). 1994; 19(18 Suppl):2041s–6s. https://doi.org/10.1097/00007632-199409151-00005 PMID: 7801181

14. Von Korff M, DeBar LL, Krebs EE, Kerns RD, Deyo RA, Keefe FJ. Graded chronic pain scale revised: mild, bothersome, and high-impact chronic pain. Pain. 2020; 161(3):651–61. https://doi.org/10.1097/j.pain.0000000000001758 PMID: 31764390

15. Carey TS, Garrett JM, Jackman A, Hadler N. Recurrence and care seeking after acute back pain: results of a long-term follow-up study. North Carolina Back Pain Project. Medical care. 1999; 37 (2):157–64. https://doi.org/10.1097/00005650-199902000-00006 PMID: 10024120

16. Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. What low back pain is and why we need to pay attention. The Lancet. 2018; 391(10137):2356–67. https://doi.org/10.1016/S0140-6736(18)30480-X PMID: 29573870

17. Downie AS, Hancock MJ, Rzewuska M, Williams CM, Lin CW, Maher CG. Trajectories of acute low back pain: a latent class growth analysis. Pain. 2016; 157(1):225–34. https://doi.org/10.1097/j.pain.0000000000000351 PMID: 26397929

18. Croft PR, Dunn KM, Raspe H. Course and prognosis of back pain in primary care: the epidemiological perspective. Pain. 2006; 122(1–2):1–3. https://doi.org/10.1016/j.pain.2006.01.023 PMID: 16530969

19. Hoy D, March L, Brooks P, Woolf A, Blyth F, Vos T, et al. Measuring the global burden of low back pain. Best Practice & Research Clinical Rheumatology. 2010; 24(2):155–65. https://doi.org/10.1016/j.berh.2009.11.002 PMID: 20227638

20. Dionne CE, Dunn KM, Croft PR, Nachemson AL, Buchbinder R, Walker BF, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. Spine. 2008; 33(1):95–103. https://doi.org/10.1097/BRS.0b013e31815e7f94 PMID: 18165754

21. Wachholtz A, Gonzalez G. Co-morbid pain and opioid addiction: long term effect of opioid maintenance on acute pain. Drug and alcohol dependence. 2014; 145:143–9. https://doi.org/10.1016/j.drugalcdep.2014.10.010 PMID: 25456326

22. Cicero TJ, Ellis MS, Kasper ZA. A tale of 2 ADFs: differences in the effectiveness of abuse-deterrent formulations of oxymorphone and oxycodone extended-release drugs. Pain. 2016; 157(6):1232–8. https://doi.org/10.1097/j.pain.0000000000000511 PMID: 27186712

23. Cicero TJ, Ellis MS, Kasper ZA. Increases in self-reported fentanyl use among a population entering drug treatment: The need for systematic surveillance of illicitly manufactured opioids. Drug and alcohol dependence. 2017; 177:101–3. https://doi.org/10.1016/j.drugalcdep.2017.04.004 PMID: 28582697

24. Cicero TJ, Ellis MS, Kasper ZA. Increased use of heroin as an initiating opioid of abuse. Addictive behaviors. 2017; 74:63–6. https://doi.org/10.1016/j.addbeh.2017.05.030 PMID: 28582659

25. Cicero TJ, Ellis MS, Kasper ZA. Relative preferences in the abuse of immediate-release versus extended-release opioids in a sample of treatment-seeking opioid abusers. Pharmacoepidemiology and drug safety. 2017; 26(1):56–62. https://doi.org/10.1002/pds.4078 PMID: 27594167

26. Cicero TJ, Ellis MS, Kasper ZA. Psychoactive substance use prior to the development of iatrogenic opioid abuse: A descriptive analysis of treatment-seeking opioid abusers. Addictive behaviors. 2017; 65:242–4. https://doi.org/10.1016/j.addbeh.2016.08.024 PMID: 27544696

27. Litman RS, Pagan OH, Cicero TJ. Abuse-deterrent Opioid Formulations. Anesthesiology. 2018; 128 (5):1015–26. https://doi.org/10.1097/ALN.0000000000002031 PMID: 29252508

28. Cicero TJ, Dart RC, Inciardi JA, Woody GE, Schnoll S, Muñoz A. The development of a comprehensive risk-management program for prescription opioid analgesics: Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®). Pain Medicine. 2007; 8(2):157–70.

29. McDaniel H, Severtson S, BucherBartelson B, Green J, Dart R. Comparing prescription opioids, methadone, and heroin endorsement rates from the treatment episode data set to the RADARS system treatment center programs. RADARS® System Technical Report. 2016:Q3.

30. We Kirch. Test of Homogeneity, Chi-Square. In: Kirch W, editor. Encyclopedia of Public Health. Dordrecht: Springer Netherlands; 2008. p. 1386–.

31. SAS Institute Inc 2013. SAS 9.4. Cary, NC

32. Dhingra L, Masson C, Perlman DC, Seewald RM, Katz J, McKnight C, et al. Epidemiology of pain among outpatients in methadone maintenance treatment programs. Drug and alcohol dependence. 2013; 128(1–2):161–5. https://doi.org/10.1016/j.drugalcdep.2012.08.003 PMID: 22951068

33. Dunn KE, Finan PH, Tompkins DA, Fingerhood M, Strain EC. Characterizing pain and associated coping strategies in methadone and buprenorphine-maintained patients. Drug and alcohol dependence. 2015; 157:143–9. https://doi.org/10.1016/j.drugalcdep.2015.10.018 PMID: 26518253

34. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. Jama. 2003; 289(18):2370–8. https://doi.org/10.1001/jama.289.18.2370 PMID: 12746360

35. Stein MD, Herman DS, Bailey GL, Straus J, Anderson BJ, Uebelacker LA, et al. Chronic pain and depression among primary care patients treated with buprenorphine. J Gen Intern Med. 2015; 30 (7):935–41. https://doi.org/10.1007/s11606-015-3212-y PMID: 25678375

36. Voon P, Hayashi K, Milloy MJ, Nguyen P, Wood E, Montaner J, et al. Pain Among High-Risk Patients on Methadone Maintenance Treatment. The journal of pain: official journal of the American Pain Society. 2015; 16(9):887–94. https://doi.org/10.1016/j.jpain.2015.06.003 PMID: 26101814

37. Barry DT, Savant JD, Beitel M, Cutter CJ, Moore BA, Schottenfeld RS, et al. Pain and associated substance use among opioid dependent individuals seeking office-based treatment with buprenorphine-naloxone: a needs assessment study. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2013; 22(3):212–7. https://doi.org/10.1111/j.1521-0391.2012.00327.x PMID: 23617861

38. Mark TL, Dilonardo J, Vandivort R, Miller K. Psychiatric and medical comorbidities, associated pain, and health care utilization of patients prescribed buprenorphine. Journal of substance abuse treatment. 2013; 44(5):481–7. https://doi.org/10.1016/j.jsat.2012.11.004 PMID: 23265445

39. Ilgen MA, Bohnert AS, Chermack S, Conran C, Jannausch M, Trafton J, et al. A randomized trial of a pain management intervention for adults receiving substance use disorder treatment. Addiction (Abingdon, England). 2016; 111(8):1385–93. https://doi.org/10.1111/add.13349 PMID: 26879036

40. Wachholtz A, Robinson D, Epstein E. Lessons Learned: Developing a Better Treatment for Patients With Chronic Pain and Opioid User Disorder. 2021.

41. Meerwijk EL, Larson MJ, Schmidt EM, Adams RS, Bauer MR, Ritter GA, et al. Nonpharmacological Treatment of Army Service Members with Chronic Pain Is Associated with Fewer Adverse Outcomes After Transition to the Veterans Health Administration. J Gen Intern Med. 2019. https://doi.org/10.1007/s11606-019-05450-4 PMID: 31659663

42. Hobelmann JG, Huhn AS. Comprehensive pain management as a frontline treatment to address the opioid crisis. Brain and Behavior. 2021:e2369. https://doi.org/10.1002/brb3.2369 PMID: 34555260

43. National Academies of Sciences E, Medicine. Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. Bonnie RJ, Ford MA, Phillips JK, editors. Washington, DC: The National Academies Press; 2017. 482 p.

44. Williamson C, Martin BJ, Argoff C, Gharibo C, McCarberg B, Atkinson T, et al. Pain Management and Opioid Therapy: Persistent Knowledge Gaps Among Primary Care Providers. Journal of Pain Research. 2021; 14:3223. https://doi.org/10.2147/JPR.S316637 PMID: 34703298

45. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. Lancet. 2019; 393(10182):1760–72. https://doi.org/10.1016/S0140-6736(18)33078-2 PMID: 30878228

46. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths—United States, 2013–2017. MMWR Morbidity and mortality weekly report. 2018; 67(5152):1419–27. https://doi.org/10.15585/mmwr.mm675152e1 PMID: 30605448