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Prescribing of Opioids and Benzodiazepines Among Patients with History of Overdose

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Abstract

Objectives: Addiction and overdose related to prescription drugs continues to be a leading cause of morbidity and mortality in the US. We aimed to characterize the prescribing of opioids and benzodiazepines to patients who had previously presented with an opioid or benzodiazepine overdose.

Methods: This was a retrospective chart review of patients who were prescribed an opioid or benzodiazepine in a one-month time-period in 2015 (May) and had a previous presentation for opioid or benzodiazepine overdose at a large healthcare system.

Results: We identified 60,129 prescribing encounters for opioids and/or benzodiazepines, 543 of which involved a patient with a previous opioid or benzodiazepine overdose. There were 404

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unique patients in this cohort, with 97 having more than one visit including a prescription opioid and/or benzodiazepine. A majority of prescriptions (54.1%) were to patients with an overdose within the two years of the documented prescribing encounter. Prescribing in the outpatient clinical setting represented half (49.9%) of encounters, while emergency department prescribing was responsible for nearly a third (31.5%).

Conclusions: In conclusion, prescribing of opioids and benzodiazepines occurs across multiple locations in a large health care system to patients with a previous overdose. Risk factors such as previous overdose should be highlighted through clinical decision support tools in the medical record to help prescribers identify patients at higher risk and to mobilize resources for this patient population. Prescribers need further education on factors that place their patients at risk for opioid use disorder and on alternative therapies to opioids and benzodiazepines.

Introduction

Opioid use disorder continues to be a leading cause of morbidity and mortality in the US. Since 1999, the prescribing of opioids as well as the number of opioid-related deaths have both nearly quadrupled (Centers for Disease Control and Prevention 2016). Despite poor evidence that opioid therapy improves pain or function in chronic noncancer pain, opioids continue to be prescribed in large quantities to this patient population (Chou et al. 2015). There is good evidence that opioid therapy is effective in multiple acute pain conditions, but the introduction of opioids to patients with these conditions has been associated with the risk of progressing to long term dependency (Hoppe et al. 2015, Shah et al. 2017). Several patient specific factors have been associated with risk of progressing to opioid use disorder, including previous psychological disorder and substance use disorder (Dufour et al. 2014).

Previous opioid overdose is a particularly high-risk characteristic in patients receiving opioids for pain. Larochelle et al. showed that 91% of commercially insured adults with a history of nonfatal overdose while on chronic opioid therapy for noncancer pain received an opioid prescription within 299 days following an opioid overdose, suggesting that risky prescribing patterns are a potential driver for the ongoing epidemic (Larochelle et al. 2015). A similar study by Naeger et al. used claims data to examine prescribing practices following opioid-related admissions and demonstrated 22% of patients filled a prescription for an opioid pain reliever and 14% filled a prescription for a benzodiazepine within 30 days post-discharge (Naeger et al. 2016). The use of insurance claims data in these studies limits the ability to further characterize the population and prescribing practices.

In addition to an increase in opioids over the past two decades, there has also been a substantial increase in the prescribing of benzodiazepines and in the prevalence of benzodiazepine use disorder. The number of prescriptions for benzodiazepines increased 67% between 1996 and 2013, while the total amount of benzodiazepines filled has more than tripled (Bachhuber et al. 2016). Overdose deaths often involve both benzodiazepines and opioids. Opioids are involved in approximately 75% of benzodiazepine overdose deaths, while benzodiazepine are involved in 31% of opioid overdose deaths (Jones and McAninch 2015). The increasing concurrent use of benzodiazepines and opioids is cited as a cause for increases in overdoses across the US (Warner et al. 2016, Sun et al. 2017).

Those who misuse oral opioid medications often fail to perceive the risk of ongoing use despite data showing high risk of overdose and death (Frank et al. 2015). Furthermore, those with concurrent use of benzodiazepines and opioids fail to perceive the increased risk of overdose (Rowe et al. 2016). Neuroscience research suggests that chronic opioid exposure may increase impulsivity and risk taking and affect risk perception in those using opioids (Baldacchino et al. 2016). This highlights the imperative of prescribers to evaluate the risk of further opioid and benzodiazepine prescribing in those who have previously overdosed.

The purpose of this study is to determine the prevalence of history of overdose among the patients being prescribed controlled substances and provide a more detailed descriptive analysis of these encounters and patients across a large healthcare system. We aim to expand on previous research by examining the characteristics of the preceding overdose, of the patient, and of the subsequent controlled substance prescribing encounter through medial record abstraction.

Methods

This study was a retrospective chart review of patients at a large healthcare system with greater than 12 million patient encounters per year. An electronic tool embedded in our EMR (CERNER™) collects data whenever a prescription for a controlled substance is written. This occurs for all controlled substance prescriptions written, including at discharge from an inpatient admission, from the emergency department, from an urgent care, or from an outpatient visit. This tool has since been used to power an alert which displays to prescribers at the point of care when a patient meets one or more of identified risk criteria for substance use disorder of opioids or benzodiazepines. A full description of the development of this tool and the selection of risk factors has been previously described (Seymour et al. 2016). One risk factor recorded in this database is a documented opioid or benzodiazepine overdose within the patient's electronic medical record (EMR) in our system, which includes data from 2007-present. Specifically, this database automatically pulls the diagnosis codes listed in Table 1. Our healthcare system includes more than 40 hospitals and over 900 care locations. All providers use a common EMR, which houses more than 7 million patient records and captures information from 2007 to present date. We used one month of data from 2015 to identify patients who were prescribed a benzodiazepine or opioid (excluding buprenorphine) during that month and had a previous presentation for opioid or benzodiazepine overdose within the large healthcare system. Patients whose original overdose was determined to be a "treatment error" (overdose which occurred even though patient took the medication as prescribed) were later excluded from this analysis. Type of pain or diagnosis were not criteria for inclusion or exclusion. Prescribers were unaware of previous overdose or patient specific risk factors unless they searched through the EMR to find this information. There were no alerts provided to the prescribers during the time of this study.

All data abstraction was performed by trained research analysts supervised by the lead author and research team. A subset of charts (n=54) was abstracted by two physicians in addition to the abstractors early in the data collection process to determine reliability of information collected and to provide guidance as necessary. During this process, the authors

found agreement on type of overdose in 63% of patients. To improve reliability, additional guidance was given to the abstractors and the case report form was changed to capture objective criteria to determine cause of overdose (i.e. whether suicide was mentioned in the notes; whether a psychiatry consult was ordered; the conclusion of the psychiatry consult; and whether the diagnosis code indicated suicide attempt), rather than having the abstractor make a subjective conclusion. A preliminary data abstraction from the EMR was performed on these patients to determine the cause of the overdose as either 1) a suicide attempt, 2) unintentional (defined as self-induced without suicidal intent), 3) treatment error (taken as prescribed), or 4) unknown. The overdose was determined to be a "suicide attempt" if a diagnosis code indicated suicide, suicide was mentioned in the physician notes, and/or the patient received a psychiatry consult which determined suicidal intention. The unintentional category includes the intention to use the opioid or benzodiazepine for reasons other than prescribed without the intention of self-harm or an overdose that occurred while taking an opioid or benzodiazepine as prescribed but while using another substance such as alcohol. This categorization was based on medical documentation by the emergency provider, inpatient providers, and any psychiatric consultations provided during the visit. Treatment errors were defined as an overdose that occurred even though the patient took the medication as prescribed. For this paper, we chose to limit the patient population to those considered suicide attempts, unintentional, or unknown (n=404). We excluded those with treatment error (n = 9) since this category is felt to be lower risk for subsequent prescribing if correct dosing is chosen. For this subgroup of patients, we performed a more detailed data abstraction to determine cause of overdose, substances involved in overdose, medication prescribed at subsequent health system encounter, location of subsequent encounter, and other comorbidities. Comorbidities were included if the condition was listed anywhere in patient's chart; they were not limited to diagnoses for the specific encounter or a specific time frame. Data were entered into REDCap electronic data capture tools hosted at Carolinas HealthCare System (Harris et al. 2009 Apr), and descriptive statistical analysis was performed with Statistical Analysis System (SAS® version 9.4, Copyright © 2012 SAS Institute Inc., Cary, NC, USA). This research study was conducted with approval of Atrium Health Institutional Review Board and did not require patient consent.

Results

Over the one-month period examined, our system had 770,431 patient encounters, of which 60,129 included a prescription for an opioid and/or benzodiazepine (Figure 1). Of these prescribing encounters, 543 involved a patient with a previous opioid or benzodiazepine overdose coded in the EMR (0.9%). There were 404 unique patients in this cohort, with 97 patients having more than one visit with a prescription during the one-month study period.

Most patients were between 35–64 years old (70.5%; mean age 46.9). Benzodiazepines without opioids accounted for 51.2% (N=207) of overdoses in this cohort, while opioids were involved alone in 74 cases or in combination with benzodiazepines in 114 cases (Table 2). We did not determine whether the opioid or benzodiazepine contributing to the overdose was a prescribed medication, nonmedical or recreational use of the medication, or an illicit substance. The leading cause of overdose was determined to be unintentional at 51.0% of the examined overdoses and suicide attempts accounted for 40.3% of the overdose. Patients in

this cohort had a high burden of mental health comorbidities with 54.5% diagnosed with anxiety and 55.2% diagnosed with depression. Additionally, comorbid diagnoses included substance use disorder (29.2%), bipolar disorder (24.0%), and schizophrenia (4.2%).

Most patient encounters (54.1%) were for patients who had received an opioid or benzodiazepine prescription within two years of the documented overdose (Table 3). Opioids were prescribed more often than benzodiazepines (71.8% vs. 23.2%, respectively). At 27 of these encounters (5.0%), patients received prescriptions for both a benzodiazepine and an opioid. Hydrocodone and oxycodone containing opioids were the most frequently prescribed medications (56.0%).

Most of these prescriptions were written in outpatient clinical settings, including outpatient primary care, specialty care, outpatient procedures(49.9%). A large subset of these outpatient encounters included prescriptions written after medical phone call consultation accounted for a significant proportion of prescribing encounters (27.4%). Emergency department prescribing also accounted for a significant proportion of prescribing (31.5%). Primary care office visits accounted for 13.1% of prescribing. Behavioral health (5.2%) and cancer care (0.7%), accounted for a small proportion of the prescribing. Out of the 543 prescribing encounters, we were able to identify diagnosis codes for 299 encounters in the billing data. There were 133 diagnosis codes identified as acute (i.e. sprain/strain, fracture) and 36 identified as chronic pain (i.e. fibromyalgia, rheumatoid arthritis) conditions; however, 90 patient encounters had no diagnosis codes associated with their encounter; 65 had diagnoses which could be classified as either acute or chronic pain (i.e. back pain). Of the patients who could easily be classified as acute or chronic pain, about two-thirds had an acute pain diagnosis. The most common diagnoses were sprain/strain, contusion, fracture, and dental pain.

Over a quarter of opioid prescribing encounters (25.9%) resulted in a daily morphine milliequivalent dose of 50 or greater (Table 4), and 38.6% were written for more than 28 days. Many of these patients had other risk factors for substance use disorder of controlled substances in addition to their history of overdose. Most notably, almost half (47.3%) of patients had a positive blood alcohol level or a positive toxicology screen for marijuana or cocaine at any time within their medical record. Additionally, 1 in 5 patients received an “early refill”, meaning that they had an active prescription documented in the EMR with more than half of the prescribed quantity (if taken as prescribed) remaining.

Hydrocodone and oxycodone containing compounds accounted for the majority (55.8%) of the medications prescribed during the subsequent encounter (Table 5). Benzodiazepines accounted for a quarter (25.5%) of the medications prescribed. Methadone, which is used for pain and may also be used for treatment of opioid use disorder, was prescribed to few patients (1.2%) in this cohort.

Discussion

High risk prescribing to patients with opioid overdose has previously been outlined in retrospective insurance claims data (Larochelle, Liebschutz et al. 2015, Naeger et al. 2016).

Our study examined detailed demographics and patient specific factors around prescribing to patients with a previous opioid or benzodiazepine overdose. The results demonstrate the occurrence of high risk prescribing of opioids or benzodiazepines in 404 unique patients over a one-month period in a large health care system. To the best of our knowledge, this is the first study to examine prescribing patterns in patients with prior overdose of benzodiazepines and/or opioids. It is of particular interest that opioids were involved in fewer than half of these overdoses, while benzodiazepines without opioids were implicated in 51% of overdoses. Benzodiazepines are known to rarely cause significant toxicity when ingested alone in an overdose (Hojer et al. 1989). However, the combination of benzodiazepines with opioids is known to be a risk factor for overdose death, and previous research suggests the longer a patient is on benzodiazepines, the higher the risk of a polysubstance overdose (Turner and Liang 2015, Bachhuber, Hennessy et al. 2016).

Having a previous overdose, whetherunintentional or by suicide attempt, presents a particularly high-risk scenario for subsequent opioid prescribing. While we found patients with previous overdose account for only 0.9% of all prescribing, the small percentage relative to the overall prescribing encounters for opioids and benzodiazepines should not diminish the significant risk for mortality specific to this population. This study represents patients in one large healthcare system over one month, but extrapolating these numbers to describe potential risk across the US over time leads to large numbers and accounts for significant morbidity and mortality. This risk is highlighted in previous research from the VA that shows 82% of patients with an opioid overdose were subsequently prescribed opioids and 25% of those patients went on to have another overdose (Boyle et al. 2017). Therefore, this high risk cohort should be identified through clinical decision support to mobilize clinicians to evaluate risk and mobilize harm reduction strategies. Risk mitigation strategies that can be employed include opioid alternative therapies to reduce daily MME in those who have opioid dependence and to avoid repeat opioid exposure in those who are not currently dependent on opioids. Additionally, naloxone co-prescribing can be implemented in this high risk group, particularly in patients that are co-prescribed benzodiazepines with opioids. Furthermore, many patients have other risk factors in addition to the previous overdose, with almost half having a history of a positive alcohol, cocaine, or marijuana toxicology screen in their medical record and this should be included in a clinical decision support tool.

Through chart abstraction, we outlined the suspected cause of overdose in the data, whether unintentional or from suicide attempt. The large number of patients with suicide attempt (40%) in this cohort highlights the complex behavioral health comorbidities that exist in this high-risk population. Mental health disorders, particularly depression and post-traumatic stress disorder, are commonly comorbid with substance use disorder and overdose (Bohnert et al. 2011, Turner and Liang 2015, Wilder et al. 2016). Not surprisingly, the risk of opioid dependence and misuse increases with comorbid mental health disorders in both acute and chronic pain (Edlund et al. 2007, Helmerhorst et al. 2014). Our study provides further evidence to the correlation of mental health disorders with substance use disorders. Our results suggest that mental health comorbidities and a history of a previous suicide attempt should motivate prescribers to consider alternatives to opioids for pain control.

Most of the prescribing after an overdose occurred in the outpatient setting, whether from outpatient clinics or emergency departments. It is unclear if prescribers were aware of the previous overdose and we were unable to obtain this information from chart abstraction. We were surprised to discover that 27.4% of the prescribing encounters occurred during a medical phone call consultation. We suspect these visits are for patients that are calling their primary prescribers for treatment after previously establishing care with that provider, as there is no clinic visit note for these encounters. Our results suggest that providers should be particularly cautious when prescribing controlled substance following a telephonic medical encounter.

Additionally, risk factors of opioid dependence and opioid use disorder were identified in the database, including positive toxicology screens in 47.3% of patients. Tobacco, cannabis, and alcohol use disorders are known to be comorbid substance use disorders in patients at risk for overdose and increase the risk of repeat overdose in this population (Edlund, Sullivan et al. 2007, Fiellin et al. 2013). Prescribers should be screening for comorbid substance use disorders in patients they are considering for opioid therapy and prioritize non-opioid therapies in this population.

The high-risk prescribing identified in our study suggests providers may not be adequately identifying risk factors present in patients who are receiving benzodiazepines and/or opioids. At least one-third of these prescriptions were given opioids for chronic conditions, suggesting that prescribers decided to either initiate or continue opioids in conditions that have poor evidence for long term improvement in function or pain from opioid therapy and despite the previously documented risk factor of overdose in the chart. The large percentage of patients (25.9%) receiving greater than 50 MME of opioids a day is particularly concerning in this cohort, given the increased risk of overdose at this daily dose. Also, the 5% of patients receiving a combination of opioids and benzodiazepines in this cohort is particularly concerning given a history of overdose and known increased risk of adverse outcomes with this combination of medications.

These results suggest prescribers may need better tools to help in identifying patients at risk for overdose and substance use disorders. The electronic tool used to identify the patients in this cohort is also being developed as a clinical decision support tool. The diagnoses listed at time of prescribing, such as sprains and strains, suggest many of these conditions could be treated with opioid sparing modalities and a next step in our ongoing investigation is to explore whether the knowledge of overdose via this EMR alert changes prescribing behavior. This data suggests more tools like this will be needed to identify patients at higher risk of opioid or benzodiazepine use disorders. Additionally, providers will need training in alternatives to opioids to managing pain. More investment in multimodal pain management will be required in this patient population.

Since this study was a retrospective chart review of prospectively identified patients, there were several limitations. First, due to the nature of this dataset, we were unable to determine the proportion of patients with a history of overdose who were prescribed a controlled substance. However, this question has already been addressed (Larochelle, Liebschutz et al. 2015). This paper sought to describe these scenarios in a more detailed fashion. This paper

did not seek to determine the "appropriateness" of the prescriptions, but rather to assess the risk involved. We did examine the diagnosis codes at the time of prescribing to better characterize this encounter but found that many of the visits were missing diagnosis codes in our dataset, limiting the accuracy of this data point. The drugs indicated as the cause of the overdose were obtained by reviewing chart documentation. Therefore, the identified cause of overdose was abstracted from the clinical determination made during the hospital visit and did not always include a laboratory analysis of blood or urine. In general, urine drug screens are commonly used in overdose patients in the clinical setting, but commonly fail to identify the causative agent due to the inability of the test to detect many of the commonly used substances. Like in the clinical setting, this retrospective study must rely on the patients' clinical presentation in addition to laboratory analysis, which may limit the accuracy in some cases. Similarly, the determination as to whether the patient made a suicide attempt or unintentionally overdosed was determined by data provided by clinician and consultants in the medical record. While it is good clinical care to inquire about the intent of an overdose, even among those who have a long history of opioid use disorder, it is unclear if providers accurately investigate the motive behind the overdose or if the patient accurately reported their motive, which may limit the accuracy of this data point. This study did not follow patients after receiving these prescriptions to detect further overdose. This should be explored in future studies to determine the risk involved in prescribing to this patient population. Finally, this analysis was limited to data within our healthcare system's electronic medical record. Therefore, diagnoses, treatments, and prescriptions from encounters outside this system were not captured.

Conclusions

In conclusion, prescribing of opioids and benzodiazepines occurs across multiple locations in a large health care system to patients with a previous overdose. These patients have a high level of comorbidities, particularly mental health disorders and substance use disorders. Risk factors such as previous overdose should be highlighted through clinical decision support tools in the medical record to help prescribers identify patients at higher risk and to mobilize resources for this patient population. Prescribers need further education on factors that place their patients at risk for opioid and benzodiazepine use disorders and on alternative therapies to opioids and benzodiazepines, particularly in high risk patients

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List of Abbreviations:

(EMR)	Electronic Medical Record

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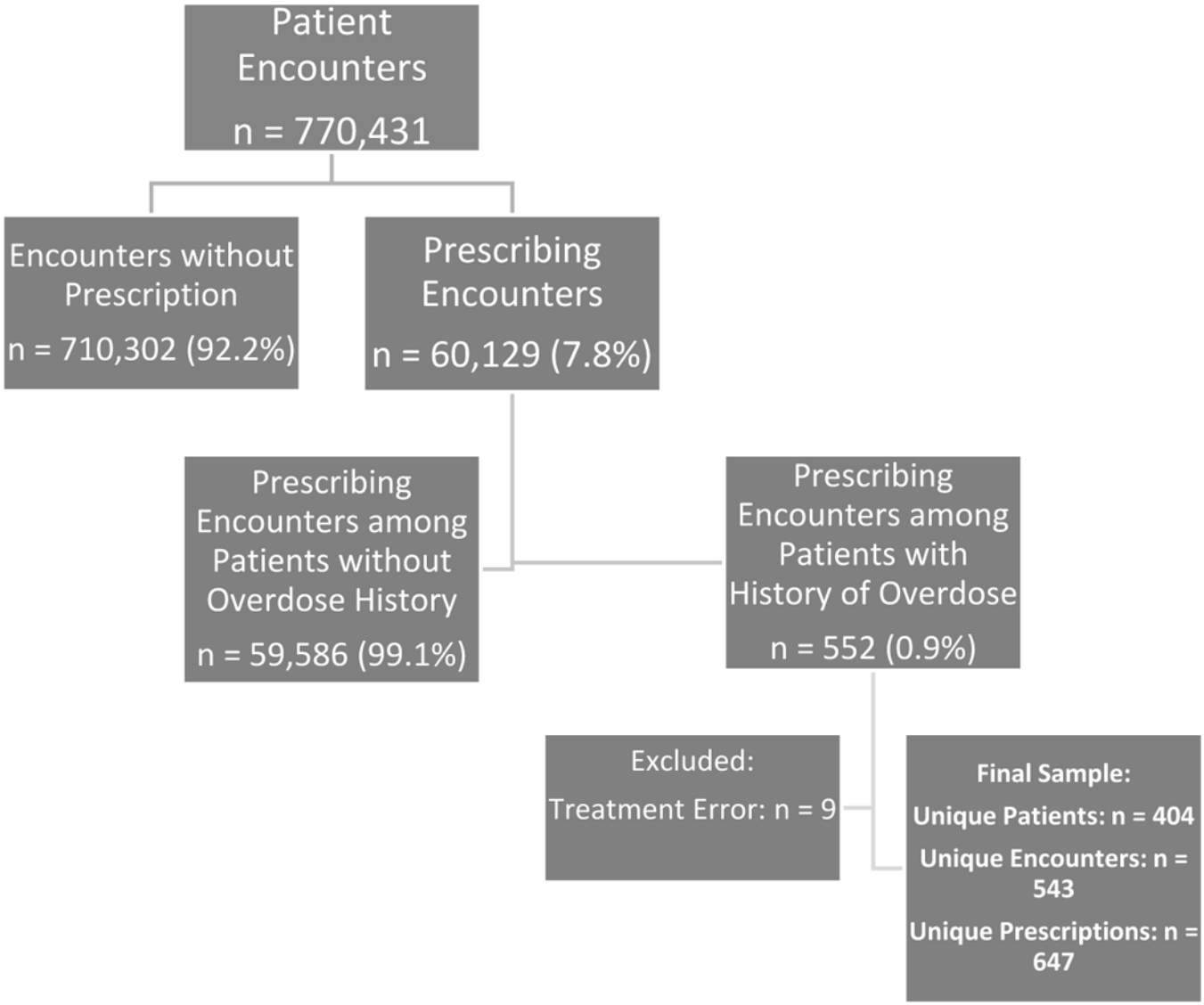

Figure 1:
Patient Selection Diagram.

Table 1.

Overdose diagnosis codes used as inclusion criteria

ICD 9	ICD 10
96509 Poisoning by opiate/related narcotic	T402X1A Poisoning by other opioids, accidental (unintentional), initial encounter T402X2A Poisoning by other opioids, intentional self-harm, initial encounter T402X3A Poisoning by other opioids, assault, initial encounter T402X4A Poisoning by other opioids, undetermined, initial encounter T404X1A Poisoning by other synthetic narcotics, accidental (unintentional), initial encounter T404X2A Poisoning by other synthetic narcotics, intentional self-harm, initial encounter T404X3A Poisoning by other synthetic narcotics, assault, initial encounter T404X4A Poisoning by other synthetic narcotics, undetermined, initial encounter T40601A Poisoning by unspecified narcotics, accidental (unintentional), initial encounter T40602A Poisoning by unspecified narcotics, intentional self-harm, initial encounter T40603A Poisoning by unspecified narcotics, assault, initial encounter T40604A Poisoning by unspecified narcotics, undetermined, initial encounter T40691A Poisoning by other narcotics, accidental (unintentional), initial encounter T40692A Poisoning by other narcotics, intentional self-harm, initial encounter T40693A Poisoning by other narcotics, assault, initial encounter T40694A Poisoning by other narcotics, undetermined, initial encounter
9694 Poisoning by benzodiazepine-based tranquilizer	T424X1A Poisoning by benzodiazepines, accidental (unintentional), initial encounter T424X2A Poisoning by benzodiazepines, intentional self-harm, initial encounter T424X3A Poisoning by benzodiazepines, assault, initial encounter T424X4A Poisoning by benzodiazepines, undetermined, initial encounter

Table 2.

Characteristics of Patients with Previous Overdose Receiving Opiate/Benzodiazepine Prescriptions (n = 404)

Variable	N	%
Age	2	0.5
<18	76	18.8
18–34	152	37.6
35–49	133	32.9
50–64	41	10.1
65+		
Average Age at Prescription	46.9 (13.4); Range: 16–87	
Average Age at Overdose	44.8 (13.5) Range: 13.9–82.2	
Cause of Overdose	206	51.0
Unintentional	163	40.3
Suicide Attempt	35	8.7
Unknown/Missing		
Overdose Substance	74	18.3
Opiate only	207	51.2
Benzodiazepine only	114	28.2
Both	9	2.2
Missing		
Comorbidities	17	4.2
Schizophrenia	97	24.0
Bipolar	220	54.5
Anxiety	223	55.2
Depression	118	29.2
Substance Use Disorder		
Number of Prescribing Encounters	307	76.0
1	65	16.1
2	24	5.9
3	6	1.5
4	2	0.5
5		

Table 3.

Characteristics of Prescribing Encounters (n=527)

Drug Prescribed	390	71.8
Opioid	126	23.2
Benzodiazepine	27	5.0
Both		
Years Since Overdose	55	10.1
0	137	25.2
1	102	18.8
2	97	17.9
3	59	10.9
4	49	9.0
5	35	6.5
6	9	1.7
7		
Location of Prescribing Encounter	28	5.2
Behavioral Health	4	0.7
Cancer	171	31.5
ED	149	27.4
Follow-up/Phone	40	7.4
Inpatient Discharge	3	0.6
Other	14	2.6
Outpatient Procedures	71	13.1
Primary Care	37	6.8
Specialty Care	8	1.5
Urgent Care	18	3.3
Unknown		
Also Had Other Risk Factors	53	9.8
3+ prescriptions	42	7.7
2+ onsite administrations	109	20.0
50% remaining (“early refill”)	257	47.3
Positive BAC or toxicology	129	23.8
BAC	139	25.6
Marijuana	88	16.2
Cocaine		

Table 4.

MME details of opiate prescriptions given to patients with prior overdose (n=417)

	Encounters with Opioids N	%
MME Daily Dose	134	32.1
0–20	163	39.1
21–49	76	18.2
50–99	32	7.7
100+	12	2.9
Missing		
MME Total	174	41.7
0–250	70	16.8
251–500	28	6.7
501–750	18	4.3
751–1000	115	27.6
>1000	12	2.9
Missing		
Average MME Total	1037 (SD = 1695) range: 15 – 10800	
Median MME Total	375 (IQR = 1088)	
Average mme/day	47.0 (SD = 48.6) range: 5.0 – 360.0	
Median MME/day	30.0 (IQR = 40)	
Average duration	19.4 (SD = 22.9) range: 1 – 180 days	
Duration	88	21.1
0–3 days	72	17.3
4–7 days	57	13.7
8–14 days	17	4.1
15–21 days	10	2.4
22–28 days	161	38.6
>28 days	12	2.9
Missing		

Table 5:

Medications prescribed at subsequent encounter, n = 647

Medication	N	%
Benzodiazepines		
LORazepam	36	5.6
chlordiazePOXIDE	3	0.5
clonazePAM	67	10.4
diazepam	13	2.0
temazepam	7	1.1
ALPRAZolam	38	5.9
Opioids		
HYDROcodone-acetaminophen	181	28.0
HYDROmorphone	8	1.2
acetaminophen-codeine	3	0.5
butalbital/ASA/caffeine/codeine	1	0.2
butorphanol	2	0.3
fentaNYL	15	2.3
methadone	8	1.2
morphine	6	0.9
oxyCODONE	80	12.4
oxyCODONE-acetaminophen	101	15.6
oxymorphone	7	1.1
tapentadol	1	0.2
traMADol	70	10.8