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Research and Applications

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Characterizing non-heroin opioid overdoses using electronic health records

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ABSTRACT

Introduction: The opioid epidemic is a modern public health emergency. Common interventions to alleviate the opioid epidemic aim to discourage excessive prescription of opioids. However, these methods often take place over large municipal areas (*state-level)* and may fail to address the diversity that exists within each opioid case (*individual-level*). An intervention to combat the opioid epidemic that takes place at the individual-level would be preferable.
Methods: This research leverages computational tools and methods to characterize the opioid epidemic at the individual-level using the electronic health record data from a large, academic medical center. To better understand the characteristics of patients with opioid use disorder (OUD) we leveraged a self-controlled analysis to compare the healthcare encounters before and after an individual's first overdose event recorded within the data. We further contrast these patients with matched, non-OUD controls to demonstrate the unique qualities of the OUD cohort.
Results: Our research confirms that the rate of opioid overdoses in our hospital significantly increased between 2006 and 2015 ($P < 0.001$), at an average rate of 9% per year. We further found that the period just prior to the first overdose is marked by conditions of *pain* or *malignancy*, which may suggest that overdose stems from pharmaceutical opioids prescribed for these conditions.
Conclusions: Informatics-based methodologies, like those presented here, may play a role in better understanding those individuals who suffer from opioid dependency and overdose, and may lead to future research and interventions that could successfully prevent morbidity and mortality associated with this epidemic.

Key words: opioid-related disorder, electronic health records, clinical informatics, epidemiology, substance-related disorders

INTRODUCTION

Characterizing the opioid epidemic from a rich and inclusive data source is a keystone for its abatement. Like the human immunodeficiency virus/Acquired immunodeficiency syndrome crisis, the opioid epidemic is a modern public health emergency. The human immunodeficiency virus/Acquired immunodeficiency syndrome epidemic reminds us that to effectively combat the opioid epidemic, clinical interventions should be tailored to treat the affected populations.[1,2]

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At present, many strategies toward abatement of the epidemic include prescription drug monitoring programs (PDMPs) or prescribing limitations. These methods aim to monitor and limit overprescription of opioids and are often enacted at the *state-level*. However, such policies can fail to address patterns that occur within the singular opioid use disorder (OUD) patient. A more informed approach to combating the epidemic would address opioid cases at the *individual-level*. A thorough, longitudinal characterization of OUD patients may support an individual-level intervention through identification of patterns of opioid misuse before and after overdose, and hold the potential for improving quality of care that *state-level* interventions may overlook.

Though there are a number of factors theorized to have caused the epidemic, the unique pharmacology of opioids and increased advocacy for pain management over the last three decades are likely contributors.[3–5] Opioids are a class of drug that includes prescription medications such as morphine, and illicit drugs, such as heroin.[6] These drugs interact with neuroreceptors to lessen pain-signal perception.[7–9] For this reason opioids remain the most commonly prescribed drug for the treatment of postoperative, cancer and noncancer pain.[10] Opioids can also cause relaxation, sedation, and euphoria[9,11] while repeated use can lead to dependence.[12,13] Acute overdose can result in bradycardia, hypotension, respiratory depression, leading to eventual respiratory and cardiopulmonary arrest resulting in death.[14]

The start of the opioid epidemic is widely cited as the mid-1990s.[15–17] There were many contributing factors, including a movement to address untreated pain from the American Pain Society,[18] use of opioids for treatment of nonmalignant pain,[19] and targeted marketing of physicians that minimized the addictive potential of these drugs.[20] The number of Americans that have been affected by opioid misuse has increased. In 2016, 2.1 million Americans were estimated to have OUD and nearly 11.8 million Americans reported opioid misuse in the previous year.[21] Between 2001 and 2016, the percentage of deaths attributable to opioids increased by 292%.[22]

In response to this crisis, law-makers, researchers, and clinicians alike have sought to alleviate rising opioid use.[23–26] Typically, interventions for the abatement of the opioid epidemic include policies enacted at the state- and federal-levels. These include, but are not limited to PDMPs and prescribing limitations.[27] PDMPs are databases that track controlled substance prescriptions within a state and alert health authorities to behaviors that may contribute to the epidemic.[28] Prescribing limitations are intended to mitigate excessive and unnecessary opioid prescribing through clinical practice guidelines.[29] Though these tactics hold promise, they are applied at the *state-* and *federal-level* and fail to address the precursor characteristics of the individual that may lead a prescription holder to develop OUD and possible overdose. A comprehensive and evidence-based intervention at the *individual-level* may be more appropriate. Such individual-level interventions often begin with a thorough characterization of the patients in the target cohort.

Target cohorts of OUD patients may be identified through many data sources. Often, characterizations of the opioid epidemic are done through the analysis of claims data[30,31] or manual review of clinical documentation.[32–35] Administrative claims data, though longitudinal, may be subject to coding biases and only captures billable encounters for the insured.[36,37] Those who abuse substances comprise a highly marginalized population, where rates of insurance may be low.[38] A recent survey estimates that 20% of adults with OUD are uninsured.[39] The sole use of administrative data may disregard a large portion of the OUD population. These omitted patients may provide valuable insight into ways to mitigate overdose. Alternatively, researchers have also engaged in manual review of medical records, but this may be a time-consuming process and more susceptible to human error than automated methods.[40,41] A characterization of opioid overdose that is both inclusive and efficient is preferred.

This research leverages the electronic health record (EHR) to study the opioid epidemic. The EHR is a rich, longitudinal data source that captures a greater variety of patients and detail than administrative data. The EHR may be coupled with informatics methodologies for efficient and accurate research. This presents a valuable opportunity to not only confirm the frequency of opioid events, but to characterize the events leading up to and following the overdose. We present data on all non-heroin opioid overdoses in the Columbia University Irving Medical Center (CUIMC) EHR. In addition to tracking the frequency of overdoses, we also contrast the healthcare utilization in the period prior to and after an individual's first overdose. The use of EHR data to investigate opioid overdoses provides not only a means to uncover overall trends overdoses, but also supports the identification of healthcare utilization trends that are common in overdose patients. By characterizing patients according to patterns in the EHR, we provide another avenue to support our understanding of the current epidemic.

MATERIALS AND METHODS

Data and computational tools

This research will leverage EHR data from the CUIMC clinical data warehouse. The clinical data warehouse contains observational clinical data for 5.37 million individual subjects from 1986 to 2017. Patients encounters are documented in the EHR at each outpatient, inpatient, and emergency department (ED) visit. Data modalities include, but are not limited to, diagnoses, clinical measurements, medications, and procedures. All CUIMC clinical data warehouse data is formatted according to the Observational Health Data Science and Informatics (OHDSI) common data model (CDM).[42] Use of CDM-formatted data will support downstream interoperability of our methods within the OHDSI community and may promote reproduction by OHDSI collaborators at other sites. The Columbia University Medical Center Institutional Review Board approved this study.

Case identification

To investigate overdoses in the CUIMC EHR, we identified all non-heroin opioid overdoses between January 1, 2006 and December 31, 2015. We mapped validated codes for non-heroin opioid overdoses[43] from *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM)[44] to OHDSI concept IDs (Table 1). Unique overdose events *(encounters)* that qualified for this review must have had at least one of these diagnosis codes in an emergency department or inpatient setting. The results of this query were used to generate our trend analysis. The encounters where then used to identify the unique set of overdose patients *(cases)* which are used for all later analyses. A single case may have multiple overdose encounters; we refer to the first of the overdoses as the *Index Event*. Other eligibility criteria for identifying *cases* includes continuous observation of at least 365 days before and 365 days after first overdose. A flow chart of the inclusion criteria when applied to CUIMC data can be found in the Supplementary File #4.

Trend analysis

The annual increasing rate of opioid overdoses is well documented.[21,32,45–51] To confirm a similar increase, we fit a single effect

Table 1. Mapping of ICD-9CM codes for opioid overdose to OHDSI CDM concept codes

OHDSI		ICD-9CM	
Concept name	ID	Concept name	ID
Poisoning by opiate AND/OR related narcotic	433083	Poisoning by other opiates and narcotics	965.09
Poisoning by opiate analgesic drug	4084011	Poisoning by opium (alkaloids), unspecified	965.00
Methadone analog poisoning	4156145	Poisoning by methadone	965.02

Poisson regression model to model the rate of opioid overdoses. The number of unique ED and inpatient admissions associated with overdoses were calculated for each calendar year (2006–2015). We similarly collected the number of all unique ED and inpatient admissions, regardless of related diagnoses. We then determined the significance of overdoses per year by modeling the probability of Y events (opioid overdoses) with $E(Y) = \mu$ during time period t. The log-linear model for the expected rate of overdose is given by

$$\log\left(\frac{\mu}{t}\right) = \beta_0 + \beta_1 \text{Year}$$

The model was run using the R (R Core Team, Vienna, Austria) package, glm, to fit generalized linear models, and significance of parameters was assessed using the Wald Chi-Squared Test.

Demographics

Unlike other data sources that may be limited in scope or incomplete, the EHR is a rich record of patient care. To supplement our confirmation of increasing opioid overdoses, we can additionally query the EHR to characterize patients over time. We present demographic data, such as age group, sex, and other variables such as, healthcare utilization, prescriptions, medical history, and death for a subset of the opioid overdose case cohort that was identified for the trend analysis. Because we are interested in a longitudinal characterization, this subset of patient's must have at least 365 days of available clinical data before and after their index event. Given the incomplete and inconsistent documentation of race and ethnicity data in the EHR, we elected to exclude this demographic feature.[52,53]

Health care utilization among the opioid-using population is an important factor to investigate, as metrics of healthcare utilization may help distinguish misuse from legitimate, but over-prescribed drugs[54–56] and addiction from drug-seeking behaviors.[57–59] We examined healthcare utilization by looking at patterns in the *encounter type*. Encounter types include, inpatient stays, outpatient appointments, and ED visits.

A known factor in the rise of the epidemic is the long-term use and misuse of prescription drugs.[60–64] To better understand patterns of prescription analgesic use, we identified three medication groups of interest that were defined by the Anatomical Therapeutic Chemical (ATC) Classification System.[65] The drug groups are *All Analgesics* (ATC N02); *Non-Opioid Analgesics* (ATC N02B); and *Opioid Analgesics* (ATC N02A). More information on these drug classes can be found in the Supplementary File #1. Any drug that is a descendant of the ATC class was included in this analysis. For each of these three medication groups, we calculated (1) the number of unique patients with a prescription, and the microaverage (average within a single patient) of (2) the number of prescriptions, (3) the duration in days of a drug, (4) the quantity of drug, and (5) the number of refills.

We also present metrics of medical history that address relevant risk factors for opioid misuse, such as surgical procedures,[66–68] substance related disorders,[69,70] traumatic injuries,[71] and death (Supplementary File #2).

Rather than presenting a single set of metrics for this case cohort, we present the same metrics over three periods of interest.[1] *The Vanilla Period*, which characterizes the steady-state healthcare utilization of patients. We defined this period to be the 6–12 months prior to each patients' first overdose.[2] *The Pre-OD Period*, which characterizes the period leading up to the first overdose. We defined this period to be the 6 months just prior to the overdose, but not including the overdose, itself.[3] *The Post-OD Period*, which characterizes the period directly following the patient's first overdose. We defined this period to be the 6 months after the overdose, but not including the overdose, itself.

To better contextualize the demographic data for the opioid case cohort, we additionally present all demographic domains for the three-time periods for the control cohort. To be eligible for the control cohort, patients must have had at least 365 days of observation, at least 1 inpatient admission, and could not have any history of substance abuse (Supplementary File #3). From all eligible controls, a random sample was selected to match the distribution of age and sex of the case cohort.

Self-controlled disproportionality analysis

Utilizing the *Vanilla Period*, *Pre-OD Period*, and the *Post-OD Period* that were defined above, we implemented a self-controlled disproportionality analysis to identify signals in conditions, procedures, and pharmacologic ingredients, both leading up to and directly after the first overdose of patients in the opioid case cohort (Figure 1). While not causal, this analysis may aid in our understanding of patterns that may warn of an impending overdose and the high-risk complications that follow.

Disproportionality analyses are often used to mine large, observational databases for signals in observed-to-expected ratios.[72–75] The self-controlled disproportionality analysis utilized herein differs from the traditional method in that each patient serves as their own control. The benefit of the self-controlled design is that patient-invariant features will not bias the results.[76–79] This is especially important when investigating opioid overdoses because long-term, chronic illnesses often require pain management with opioids. To better understand patterns leading up to the first overdose, we compared the *Pre-OD Period* with the *Vanilla Period*, which we call the *Pre-OD Analysis*. We then completed the *Post-OD Analysis*, which compared the *Post-OD Period* with the *Vanilla Period* to understand the window immediately following overdose. For each of these two experiments, we undertook three disproportionality analyses to look at exposure signals in (1) conditions, excluding overdose-related concepts and their descendants, (2) procedures, and (3) medications at the ingredient level.

In both experiments, the data was queried and later analyzed according to a contingency table preparation. For each period in an experiment, the observed exposure frequency was recorded as the

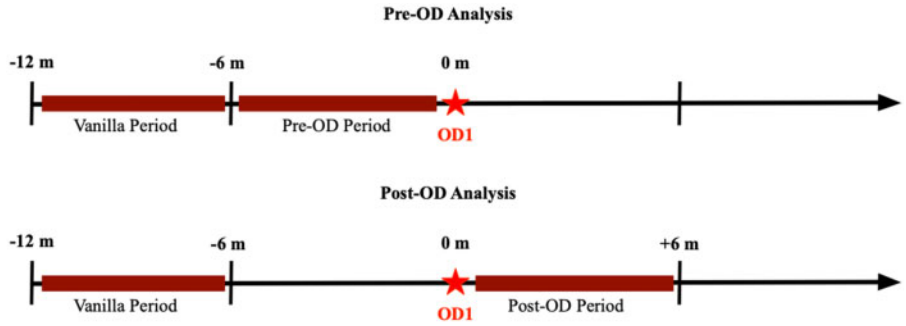

Figure 1. Schematic of self-controlled disproportionality analysis.

count of patients with that exposure in that period. For both experiments, the odds ratio (OR) and 95% confidence interval (CI) for each exposure was calculated. Exposures with zero counts that resulted in infinite ORs were excluded.

Heatmap visualization of disproportionality analysis

To better understand patterns in conditions that precede and succeed an overdose, data from the self-controlled disproportionality analysis was further analyzed to highlight how comorbidities change over time. For all conditions, we calculated average per-patient rate of occurrence, for each month in the 12 months prior to overdose (*Vanilla + Pre-OD Period)* and in the 6 months after overdose (*Post-OD Period)*. The rate for each condition was then normalized by the absolute difference between the (1) mean of that conditions monthly rate in the *Post-OD Period*, which we call the *Macro Mean Post-OD;* and (2) the mean of that conditions monthly rate in the *Vanilla + Pre-OD* Period, which we call the *Macro Mean Vanilla + Pre-OD*.

We calculated the difference between the *Macro Mean Post-OD* and the *Macro Mean Vanilla + Pre-OD* for each condition. To facilitate interpretation of this visualization, we reduce the presented output and present the 10 conditions with the highest difference in Macro Means and the 10 conditions with the lowest difference in Macro Means. The highest difference in Macro Means were positive, indicating an increased occurrence of this condition in the *Post-OD Period*, relative to the *Vanilla + Pre-OD Period*. The lowest difference in Macro Means were negative indicating an increased occurrence of this condition in the *Vanilla + Pre-OD Period*, relative to the *Post-OD Period*.

RESULTS

Case identification

Within the study period, there were 9 498 646 patient encounters to NewYork-Presbyterian Hospital. Of these patients, 502 (0.005%) were assigned a diagnosis code associated with a non-heroin opioid overdose in an inpatient or emergency department setting. We believe this estimate to be low, as calculation of this prevalence includes outpatient encounters where acute opioid overdose is highly unlikely. These encounters correspond to 434 unique patient cases, of which 379 (87.3%) met the eligibility criteria for inclusion in our analyses.

Trend analysis

Our trend analysis confirms that, in the years 2006 through 2015, the ratio of opioid overdoses out of all hospital encounters significantly increased ($P < 0.001$), at an average rate of 9% per year (95% CI, 5.7–12.5). A plot of the opioid overdose rate over time is shown in Figure 2.

Demographics

The results of the demographics analysis are shown in Table 2. Across all periods and medication types, a greater number of opioid overdose cases had prescriptions for analgesic drugs than the controls. Overdose patients had an increased prevalence of *Opioid Analgesics (ATC N02A),* and higher microaverages of number of prescriptions, days' duration of medication, and quantity per prescription associated with this drug type. The prevalence of an opioid prescription increases from 16% in the *Vanilla Period* to 26% in the *Pre-OD Period* for cases. However, the prevalence in the case cohort continues to rise to 30% in the Post-OD period.

Self-controlled disproportionality analysis

The results of the self-controlled disproportionality analysis are shown in Table 3. The top conditions, procedures, and ingredient-level drugs are ranked by decreasing significance, which is given by the lower bound of the 95% CI. In both the *Pre-OD* and *Post-OD Analyses,* the highest odds condition is *altered mental status,* with a *Pre-OD* OR of 12.74 (2.99–24.32) and a *Post-OD* OR of 22.24 (5.33–92.73). Similarly, *computerized axial tomography of head* is the highest odds procedure in both analyses, with a *Pre-OD* OR of 8.85 (2.65–29.57) and a *Post-OD* OR of 11.56 (3.51–38.08). No medications were found to be significant in either analysis.

Heatmap visualization of disproportionality analysis

To better understand the significance of our self-controlled disproportionality analysis results, and the progression of opioid overdose, we additionally visualized the monthly disproportionality analysis data with a heatmap. The conditions with high absolute mean difference in normalized rates in the *Vanilla & Pre-OD Period* (*Macro Average Vanilla & Pre-OD*) and the *Post-OD Period* (*Macro Average Post-OD*) are shown in Figure 3.

DISCUSSION

The opioid epidemic continues to be a public health emergency. While many interventions have focused on rural areas, urban rates of overdose are on the rise.[21] Our research demonstrates that the epidemic is well represented in New York City. Between 2006 and 2015, the rate of opioid overdoses at CUIMC significantly increased, at an average annual rate of 9%. We believe this finding to be generalizable to other NYC hospitals, as our rate of inpatient and

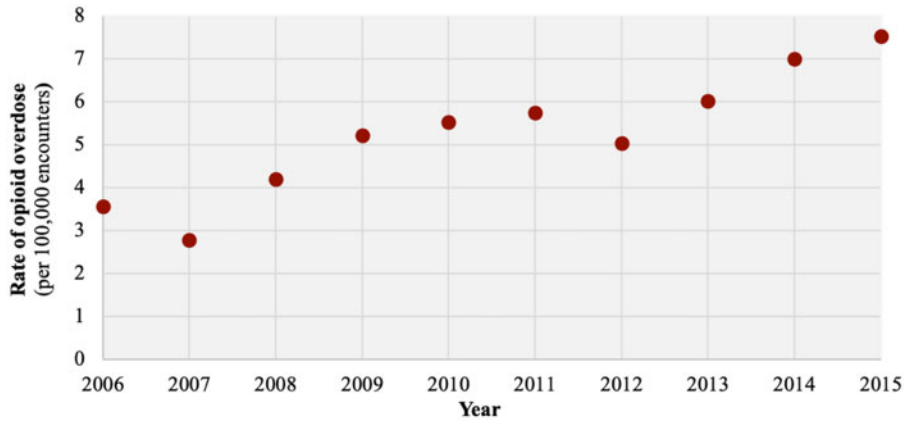

Figure 2. Rate of opioid overdoses per 100,000 hospital encounters over years 2006-2015.

Table 2. Demographics, healthcare utilization, medication use, and medical history in control and opioid case cohort under varying periods

	Random matched sample of OD−	All OD+	Vanilla Period (−12 to −6 mo)	Pre-OD Period (−6 to 0 mo)	Post-OD Period (0 to +6 mo)
N =	379	379			
Age at first OD (years)					
<18	13	13			
18–25	38	38			
>25	317	317			
Unknown	11	11			
Sex					
Male	235	235			
Female	144	144			
Average # of visits/year					
All visits	11.5		12.1	11.2	11.6
Inpatient	3.6		3.3	3.4	3.5
Outpatient	10.4		14.4	12.0	12.2
Emergency department	4.1		4.4	5.1	5.2
Medications					
All analgesics (ATC N02)					
# of people with Rx	70 (18%)		107 (28%)	177 (47%)	210 (55%)
Rx/person[a]	0.93		1.85	3.07	3.84
Days duration/person[a]	13.46		10.91	9.12	12.88
Quantity/person[a]	28.65		40.25	41.62	41.73
# refills/person[a]	1.35		0.62	0.29	0.45
Non-opioid analgesic (ATC N02B)					
# of people with Rx	70 (18%)		97 (26%)	166 (44%)	192 (51%)
Rx/person[a]	0.79		0.98	1.73	2.26
Days duration/person[a]	14.54		12.15	9.67	15.65
Quantity/person[a]	28.63		36.12	42.72	40.85
# refills/person[a]	1.50		0.69	0.40	0.66
Opioid analgesic (ATC N02A)					
# of people with Rx	32 (8%)		60 (16%)	99 (26%)	112 (30%)
Rx/person[a]	0.26		1.11	1.70	1.91
Days duration/person[a]	6.44		7.26	8.39	8.67
Quantity/person[a]	31.59		42.17	55.11	40.40
# refills/person[a]	0.67		0.00	0.12	0.07
History					
Surgical procedure	58 (15%)		46 (12%)	73 (19%)	70 (18%)
Substance-related disorder					
Alcohol-related	0 (0%)		30 (8%)	49 (13%)	82 (18%)
Drug-related	0 (0%)		79 (21%)	119 (31%)	198 (22%)
Traumatic injury	20 (5%)		30 (8%)	48 (13%)	54 (14%)
Post-OD death rate					0.005

OD: overdose; OD+: positive for opioid overdose; OD−: negative for opioid overdose; Rx: prescription; #: number; ATC: Anatomical Therapeutic Chemical class.

[a]Microaverage.

Table 3. Results of the self-controlled disproportionality analyses

	Pre-OD analysis			Post-OD analysis		
	Concept	OR	95% CI	Concept	OR	95% CI
Top conditions	Altered mental status	12.74	2.99–54.32	Altered mental status	22.24	5.33–92.73
	Disturbance of consciousness	6.70	1.50–29.88	Acute respiratory failure	13.15	4.01–43.10
	Suicidal thoughts	3.86	1.27–11.75	Suicidal deliberate poisoning	16.79	3.99–70.68
	Schizoaffective schizophrenia	5.11	1.11–23.47	Pneumonitis due to inhalation of food or vomitus	8.47	2.53–28.39
	Depressive disorder	1.62	1.05–2.51	Suicidal thoughts	6.34	2.18–18.45
	Bipolar disorder	2.00	1.03–3.88	Acidosis	8.85	2.03–38.59
	Type 2 diabetes mellitus	1.61	1.01–2.58	Disturbance of consciousness	8.85	2.03–38.59
	Essential hypertension	1.44	0.99–2.10	Conduction disorder of the heart	5.78	1.97–16.93
	Psychotic disorder	2.17	0.97–3.87	Schizoaffective schizophrenia	8.31	1.90–36.39
Top procedures	Computerized axial tomography of head	8.85	2.65–29.57	Computerized axial tomography of head	11.56	3.51–38.08
	Insertion of endotracheal tube	6.61	1.94–22.55	Diagnostic ultrasound of heart	6.43	2.47–16.76
	Continuous invasive mechanical ventilation for less than 96 consecutive hours	7.23	1.63–32.04	Diagnostic ultrasound of peripheral vascular system	5.22	1.77–15.43
	Other puncture of vein	2.46	1.57–3.84	Other puncture of vein	2.68	1.72–4.16
	Collection of venous blood by venipuncture	2.37	1.52–3.71	Collection of venous blood by venipuncture	2.59	1.66–4.03
	Diagnostic ultrasound of heart	3.73	1.37–10.15	Injection of anticoagulant	7.23	1.63–32.04
	Electrographic monitoring	10.24	1.30–80.43	Therapeutic, prophylactic, or diagnostic injection	3.65	1.45–9.14
	Injection or infusion of electrolytes	10.24	1.30–80.43	Computerized axial tomography of thorax	11.30	1.45–87.96
	Therapeutic, prophylactic, or diagnostic injection	2.31	1.24–4.34	Therapeutic, prophylactic, or diagnostic injection	2.46	1.32–4.60
Top ingredient-level drugs	Albuterol	3.02	0.31–29.13	Methadone	1.82	0.60–5.48
	Methadone	0.80	0.21–2.99	Albuterol	5.05	0.59–43.46
	Ipratropium	2.01	0.18–22.21	Glucose	0.66	0.11–4.00
	Tiotropium	1.00	0.06–16.05	Tiotropium	1.00	0.06–16.05
	Clonidine	1.00	0.06–16.05	Prednisone	1.00	0.06–16.05

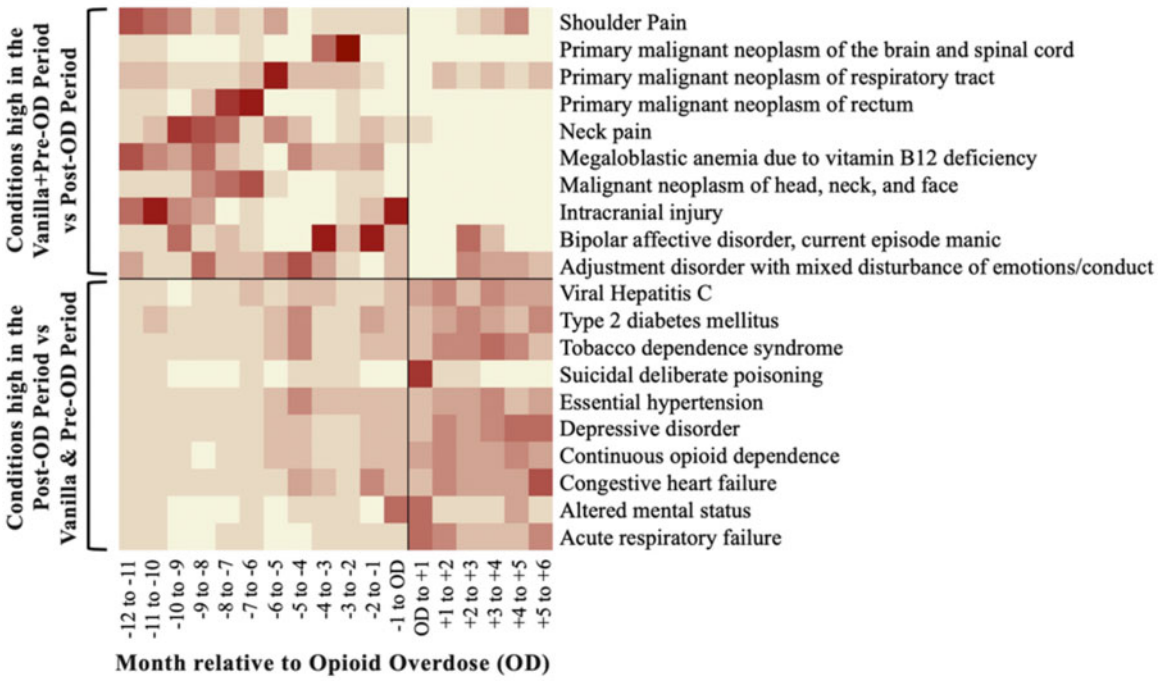

Figure 3. Heatmap of the 10 highest condition rates per month in the Vanilla & Pre-OD period and the Post-OD period.

emergency department overdoses coincides with the rates reported for New York City.[80]

The results of our demographics analysis demonstrate that our case cohort is similar in many respects to published research on this disease process.[80] Our cohort was predominantly adult patients greater than 25 years old (84%) and male (62%).

A larger proportion of cases had prescriptions for analgesic drugs in all study periods compared to the control. When examining Opioid Analgesic (ATC N02A), 8% of the controls held prescriptions for this medication class, while those cases had notably increased opioid prescriptions in all study periods (16%–30%). This implies that those with opioid prescriptions are at increased risk for overdose.[81] Surprisingly, the proportion of patients with Opioid Analgesic prescriptions increased with each study period. This may imply that the prescribing providers were unaware of prior overdoses and existing opioid prescriptions, possible because New York's PDMP requirement did not go into effect until 2013. Additionally, while both the cases and controls had durations of prescriptions outside the CDC recommended period of 3 days for acute pain,[82] we see longer durations with the opioid cases, with an average of 8.39 days in the *Pre-OD Period* and 8.67 days in the Post-OD period. This suggests that longer duration of opioid prescriptions can be associated with overdose events.

The self-controlled disproportionality analyses, *Pre-OD Analysis* and *Post-OD Analysis*, highlight trends in procedures, medications, and conditions that characterize the progression of our opioid case population.

Procedures

The high-odds procedures in the *Pre-OD Analysis,* such as *computerized axial tomography of head, insertion of endotracheal tube, diagnostic ultrasound of the heart, electrographic monitoring*, and *continuous invasive [mechanical ventilation*], may indicate that a traumatic injury, intensive care medical treatment, or scheduled surgical procedure took place just prior to the first opioid overdose. Traumatic injuries and surgical procedures have been associated with continued opioid use,[83] though we cannot demonstrate causality here. Similar high-odds procedures are seen in the *Post-OD Analysis*, which may indicate that further traumatic injuries, or evaluations for toxidromes and altered mental states are associated after overdose, as well.

Diagnostic imaging, such as *computerized axial tomography of head*, may be part of the workup for mental status changes in the absence of other identifiable causes.[84] Subsequent traumatic injuries, psychiatric evaluations, or overdoses may be the attributable to the increase in odds of many diagnostic images from the *Pre-OD* to the *Post-OD Period*. In the *Post-OD Analysis*, we also see *diagnostic ultrasound of peripheral vascular system*, which was not present in the other experiment. There is a well-documented transition from prescription opioid abuse to intravenous heroin,[85] which increases risk of venous sclerosis and the need for this procedure.

In general, the associations we have identified between procedures and opioid overdose cannot impart causality. However, procedure codes represent a unique perspective on clinical care that is worthy of analysis. Unlike medications or diagnosis codes which may follow patients through various episodes of care, procedures are predominantly associated with a distinct encounter—such as a chest x-ray during an emergency department visit—and usually required for billing. Therefore, we can have a high level of confidence in trends we have identified in our results, despite uncertainty in their cause. Further research on the relationships between opioid overdoses and procedures could aid in our understanding of this complex and at-risk patient population.

Ingredient-level drugs

Our results demonstrate that no medications at the ingredient-level were found to be significant in either our *Pre-OD* or *Post-OD* experiment, though we find interest in the relative rank of methadone *Post-OD*. Methadone is a synthetic opioid typically used for medication-assisted therapy (MAT) of OUD.[86] In the *Pre-OD Analysis*, methadone is the second most common ingredient, with a non-significant OR estimate of 0.80. In the *Post-OD Analysis*, methadone is the highest rank ingredient, with an estimated OR of 1.82. The change in both the rank and the estimate, though nonsignificant, indicates possible actions to treat OUD with MAT. The increase in MAT, coupled with the increase in opioid prescriptions seen in the *Demographics Analysis,* may indicate the presence of two cohorts: one where patients continue opioid use after overdose, and one where patients seek treatment with MAT.

Conditions

Our results from the self-controlled disproportionality analysis of conditions highlight the close relationship between drug abuse and mental health.[87,88] High OR conditions, such as *altered mental status, suicidal thoughts, schizoaffective schizophrenia, bipolar disorder, suicidal deliberate poisoning, and psychotic disorder* are common in both the *Pre-OD* and *Post-OD* Analyses. However, conditions that typically result from overdose are unique to the Post-OD period; these include *acute respiratory failure*,[89,90] *pneumonitis due to inhalation of food or vomitus*,[91] *acidosis*,[92] and *conduction disorder of the heart*.[93]

Heatmap visualization of disproportionality analysis

Conditions that traditionally merit opioid prescription have disproportionately higher rates in the *Vanilla + Pre-OD Period* than the *Post-OD Period*. These include conditions of (1) pain, such as *shoulder pain* and *neck pain,* (2) cancer-related conditions, such as *primary malignant neoplasm of the brain and spinal cord; respiratory track; rectum;* and *head, neck, and face,* (3) and injury, shown here as *intracranial injury*. We also see mental health conditions of *bipolar (affective)* and *adjustment (disorder)*. These results are contrasted by the *Post-OD Period*, where we see many condition associated with (1) prolonged opioid misuse, such as *acute respiratory failure*, *congestive heart failure*, *viral hepatitis C*,[94] and *continuous opioid dependence*, and (2) continuing mental health issues, including *suicidal deliberate poisoning*; *depressive disorder*; and *altered mental status*. This visualization of the self-controlled disproportionality analysis data highlights that the *Vanilla + Pre-OD Period* is marked by high pain conditions, which may suggest that opioid overdose stems from pharmaceutical opioids prescribed for the treatment of these conditions. The *Post-OD Period* is distinguished by complications of prolonged opioid use. However, in both Periods, mental health appears to be a strong associational condition to overdose.

LIMITATIONS

This research has some limitations. As with all analyses of EHR data, the results of this research may be both biased by the inaccurate or incomplete recording of clinical encounters, or may be reflective of institutional practices that impede generalizability.[95,96]

The results presented in this article represent only a single site, and as such the external validity of these findings are limited. In our self-controlled disproportionality analysis, because we were interested in characterizing the *Post-OD Period*, we restricted our inquiry to non-fatal opioid cases. As such, patients with fatal overdoses are not characterized. Additionally, the span of time assigned to the *Vanilla*, *Pre-OD*, and *Post-OD Periods* was somewhat arbitrary. More informative windows may exist. Furthermore, this is a retrospective analysis, and as such, strong assumptions and specialized methodology would be required to investigate causal relationships.

CONCLUSIONS

This research characterizes OUD patients, their care trajectory near an overdose event, and may illuminate aspects of the opioid epidemic. Using the EHR data at CUIMC, we are able to confirm a rise in non-heroin opioid overdoses. Unlike characterizations of the epidemic, our use of the EHR and informatics methodologies provides invaluable insights into the overdose patients and characteristics of their healthcare utilization surrounding the first, nonlethal overdose. The results of this analysis suggest that on the individual-level, the continuum of the epidemic may begin with condition occurrences associated with pain that may be tied to legitimate opioid prescriptions. This finding suggests that clinicians should consider the possibility that OUD may develop in medically necessary scenarios, and lead to an overdose in the short term. The patterns in condition diagnosis and drug prescription may also be used to inform policies surrounding the opioid-epidemic.

This research further suggests that the medical and research communities should explore informatics methods for novel ways to explore this epidemic. Ubiquitous and computable data sources, like the EHR, may allow researchers to study a wider breadth of patients and efficiently analyze their characteristics. When coupled with established informatics-based methodologies, like those presented here, the EHR may be able to play a role in better understanding those individuals who suffer from OUD and overdose. A better understanding of the events and medically relevant characteristics associated with patients with OUD may lead to future research and interventions that could successfully prevent morbidity and mortality associated with the epidemic.

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AUTHOR CONTRIBUTIONS

BS conceived of the study. BS, AA, and AP designed the study. AA created the cohorts, performed the analysis, drafted the manuscript, and designed the figures. BS, AT, DV, and AP provided critical feedback and helped shape the research, analysis and manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Journal of the American Medical Informatics Association online.

COMPETING INTERESTS

None declared.

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