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Co-Occurring Opioid Use and Depressive Disorders: Patient Characteristics and Co-Occurring Health Conditions

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ABSTRACT

Objective: Among persons with opioid use disorder (OUD), co-occurring depression is linked to a greater risk of opioid misuse, overdose and suicide. Less is known about characteristics and other comorbid health conditions of persons with co-occurring opioid use and depressive disorders. **Methods:** This study used electronic health record (EHR) encounters from the Geisinger Health System prior to the fall of 2019. Adult patients were recruited from a medication-based treatment clinic and had an OUD diagnosis ($N = 692$). Co-occurring depression was defined by a depression diagnosis in the EHR. Multivariable logistic regression was performed to assess differences in characteristics, behavioral health and medical diagnoses, as well as opioid overdose and suicide attempt or ideation between individuals with and without comorbid depression. **Results:** Forty-seven percent of patients with OUD had a lifetime depression diagnosis. Individuals with co-occurring depression were more likely to be female and have comorbid chronic pain or other medical conditions. Co-occurring depression was associated with an increased likelihood of other mental health and substance use disorders, as well as opioid overdose and/or suicide attempt or ideation. **Conclusions:** While it is established that co-occurring depression is associated with increased risk of overdose and suicide, this study adds that other health conditions, including chronic pain and common medical conditions, are more prevalent among persons with co-occurring depressive disorders. Results highlight the need to consider these complex health needs when developing treatment plans and services.

In 2019, 1.6 million people in the United States had an opioid use disorder (OUD) (Substance Abuse and Mental Health Services Administration, 2020). As with other substance use disorders, psychiatric comorbidity is relatively common among persons with OUD. Data from the National Survey on Drug Use and Health, 2015–2017 indicate that among adults with OUD, 64.3% had a mental illness in the past year (Jones & McCance-Katz, 2019); higher than that of adults with any substance use disorder (49.2% in 2019) and the US adult general population (17.7% in 2019) (Substance Abuse and Mental Health Services Administration, 2020). While more recent data is not available, major depressive disorder (MDD) is strongly associated with substance use disorders (SUDs) and

OUD in particular. From US national survey data, lifetime prevalence of co-occurring OUD and MDD has been shown to be as high as 50–60% (Conway et al., 2006; Grella et al., 2009). In OUD treatment seeking or enrolled populations, the current prevalence of MDD ranges between 20% and 30% (Goldner et al., 2014; Savant et al., 2013).

Psychiatric comorbidity among persons with SUDs is associated with reduced health-related quality of life, increased severity of mental health and substance use symptoms, higher utilization of the emergency department, and increased barriers to treatment (Bradizza et al., 2006; Compton et al., 2003; Curran et al., 2008; Krawczyk et al., 2017; Lozano et al., 2017; Mojtabai et al., 2014). Specific to depression, co-

occurring depression is associated with increased risk of opioid misuse, as well as overdose and suicide (Bartoli et al., 2014; Boscarino et al., 2016; Campbell et al., 2018; Compton et al., 2003; Krawczyk et al., 2020; Oquendo and Volkow, 2018).

Despite extensive research examining co-occurring mental health and substance use disorders, limited research has examined specific co-occurring disorders including OUD and depression. One example is a study published in the early 1990s using data from the Epidemiologic Catchment Area (ECA) study. The researchers found that among persons with OUD, 31% had an affective disorder including MDD (Regier et al., 1990). However, most prior research has examined psychiatric comorbidity overall, and because of this we know less about the characteristics and health conditions of persons with co-occurring OUD and depression, in particular. To address this gap, the current study aimed to describe characteristics and comorbid health conditions among patients with co-occurring opioid use and depressive disorders, and assess how these might differ among patients who have OUD without a depressive disorder.

Methods

Study design and sample selection

Data for this retrospective observational study was drawn from electronic health records (EHR) for all encounters prior to September 2019 for patients from the Geisinger Health System, an integrated health system serving three million patients across 45 counties in central Pennsylvania. Geisinger is an integrated health system, meaning that all primary and specialty care visits are housed within the same electronic health record. When Geisinger built its addiction medicine clinics in 2017, it was determined that in order to provide comprehensive care of a patient, addiction medicine records should also be part of the patient's comprehensive record (Barbour et al., 2020). The study sample included patients recruited from regularly scheduled appointments at a medication-based addiction treatment clinic to participate in a prospective study aimed at assessing clinical and genetic risk factors for OUD. Patients seeking treatment at the clinic signed authorization for their addiction treatment records to be part of their integrated health record. In addition, as part of this larger prospective study, all patients consented to disclosure of their health record data for research purposes. Patients seen at Geisinger's medication-based treatment clinics were primarily from self-referral but could also have been referred to treatment based on clinical referral from within or outside the health system. More information on these clinics can be found elsewhere (Barbour et al., 2020). In addition to information on encounters and diagnostic codes from the EHR, dispensed medication data was used. Past 24-month dispensed medication history from within and outside of Geisinger was extracted from Surescripts at the request of a medical provider. Dispensed medication information was available for most patients ($n = 670$, 96.8%).

The study sample was limited to patients who had an OUD diagnosis as defined by having at least one International Classification of Diseases ninth or tenth revision (ICD-9 or ICD-10) diagnostic code in their EHR from all health encounters within Geisinger. All patients were at least 18 years old at the date of their first OUD diagnosis.

A comprehensive list of all ICD-9 and -10 codes used for each diagnosis is included in Supplemental Table 1. Inclusion of ICD codes was based on previous literature (Boscarino et al., 2016; Fiest et al., 2014; Hedegaard et al., 2017; Ingram et al., 2020; Krawczyk et al., 2020; McGinty et al., 2018; Simon et al., 2018; Tian et al., 2013; Tonelli et al., 2016; Walkup et al., 2012). The current study does not qualify as human subjects research as determined by Geisinger and Johns Hopkins Bloomberg School of Public Health Intuitional Review Boards.

Study measures

Independent variables

Patients were defined as having co-occurring depressive disorder if they had at least one ICD-9 or -10 code for a depressive disorder in the EHR. Patients were excluded if the date of their first depression diagnosis occurred 0–14 days after the date of their first suicide ideation or attempt (if occurred) to exclude patients who might have received a depression diagnosis when they contacted services for suicide attempt or ideation. This resulted in an exclusion of 29 patients whose first depression diagnosis occurred on the same day as their first suicide attempt or ideation. Also, to ensure that our results did not change with a stricter case definition, we conducted sensitivity analyses using a criterion of at least three ICD codes for depression, as well as for OUD over the study period to identify patients with opioid use and depressive disorders.

Dependent variables

Opioid overdose included all poisoning codes involving opioids. *Other mental disorder* diagnoses included

Table 1. Sample Characteristics and Differences Between Patients With Opioid Use Disorder With and Without Lifetime Depression

	Overall (N = 692) %	OUD only (n = 367) %	OUD + DEP (n = 325) %	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[a,b]
Sex					
Female	48.3	39.2	58.5		
Male	51.7	60.8	41.5	0.46 (0.34, 0.62)***	0.48 (0.35, 0.66)***
Age[c]					
18–29	35.7	36.2	35.1	1.00	1.00
30–39	37.1	39.0	35.1	0.93 (0.65, 1.32)	0.88 (0.60, 1.28)
40–49	15.6	14.7	16.6	1.17 (0.74, 1.83)	1.10 (0.68, 1.81)
50 or older	11.6	10.1	13.2	1.36 (0.82, 2.25)	1.49 (0.86, 2.59)
Race					
Other	1.0	1.1	0.9		
White	99.0	98.9	99.1	1.18 (0.26, 5.32)	0.31 (0.03, 3.25)
Ethnicity					
Hispanic or Latino	2.6	3.3	1.9		
Not Hispanic or Latino	97.4	96.7	98.1	1.80 (0.67, 4.84)	0.86 (0.27, 2.76)
Marital status					
Not married	85.1	84.9	85.2		
Married	14.9	15.1	14.8	0.98 (0.64, 1.49)	0.90 (0.57, 1.44)
Geisinger insurance					
No	46.6	49.3	43.5		
Yes	53.4	50.7	56.5	1.26 (0.94, 1.71)	1.19 (0.86, 1.66)
Opioid overdose[d]					
Zero	90.8	95.1	85.9		
One or more	9.2	4.9	14.1	3.20 (1.81, 5.64)***	3.81 (2.04, 7.14)***
Other MH disorder dx[e]					
Zero	38.6	60.5	13.9		
One or more	61.4	39.5	86.1	9.53 (6.53, 13.90)***	7.05 (4.73, 10.50)***
Other SU disorder dx					
Zero	18.4	29.7	5.5		
One or more	81.6	70.3	94.5	7.21 (4.26, 12.19)***	4.95 (2.82, 8.68)***
Suicide attempt dx					
Zero	95.8	98.4	92.9		
One or more	4.2	1.6	7.1	4.58 (1.84, 11.40)**	3.58 (1.37, 9.40)**
Suicide ideation dx					
Zero	92.9	99.2	85.9		
One or more	7.1	0.8	14.1	20.01 (6.16, 64.99)***	19.79 (5.86, 66.89)***
Suicide attempt or ideation dx					
Zero	90.3	97.5	82.2		
One or more	9.7	2.5	17.8	8.64 (4.21, 17.75)***	7.92 (3.74, 16.78)***
Chronic pain dx					
Zero	38.0	52.6	21.5		
One or more	62.0	47.4	78.5	4.04 (2.89, 5.65)***	2.54 (1.75, 3.70)***
HIV or Hep C dx					
Zero	81.4	84.7	77.5		
One or more	18.6	15.3	22.5	1.61 (1.09, 2.37)*	1.31 (0.86, 2.00)
Other med dx[f]					
Zero	59.0	70.0	46.5		
One or more	41.0	30.0	53.5	2.69 (1.97, 3.68)***	1.94 (1.37, 2.76)***
Dispensed bup rx[g]					
Zero	7.5	6.3	8.7		
One or more	92.5	93.7	91.3	0.71 (0.40, 1.27)	0.64 (0.33, 1.23)
Dispensed anti-dep rx[g]					
Zero	29.0	45.4	11.2		
One or more	71.0	54.6	88.8	6.61 (4.40, 9.91)***	6.05 (3.92, 9.33)***

***p < .001, **p < .01, *p < .05.

Note. OUD = opioid use disorder; OUD + DEP = opioid use disorder and depression; OR = odds ratio; aOR = adjusted odds ratio; MH = mental health; SU = substance use; HIV = human immunodeficiency virus; Hep C = hepatitis C; dx = diagnosis; med = medical; bup = buprenorphine; anti-dep = anti-depressant; rx = prescription medication.

[a]Odds of each characteristic, diagnosis, and dispensed medication in the OUD with depression group relative to the odds of each in the OUD without depression group.

[b]Adjusted models include age, sex, race, ethnicity, number of encounters per year, and total length of care between first and last GHS encounter dates.

[c]Age at first opioid use disorder diagnosis.

[d]Includes any opioid poisoning ICD9 or ICD10 code.

[e]Excludes depressive disorders, but includes other mood disorders (53.9% have at least one mood disorder dx).

[f]Includes hypertensive disease, diabetes mellitus, and other disorders of the airway (i.e., COPD and asthma) ICD9 or ICD10 codes.

[g]Only among those with dispensed medication records, n = 670.

codes for all non-depressive mental disorders. *Other substance use* included all SUD codes other than OUD. *Chronic pain* included ICD codes for chronic pain

unspecified and the following conditions: lower-back pain, headache, fibromyalgia, arthritis and neuropathic pain (McGinty et al., 2018). To define *other medical*

diagnoses, codes for the following conditions were included: hypertension, diabetes mellitus, and disorders of the airway (chronic obstructive pulmonary disease (COPD) and asthma). These conditions were selected based on prior research examining multimorbidity among persons with substance use disorders (Salter et al., 2011). Two suicide-related diagnoses were assessed, including attempts and ideations based on corresponding codes (Table 1).

Dispensed medications. Patients were identifying as having at least one buprenorphine and/or antidepressant medication if they had at least one of these types of medications in their dispensed records.

Demographic information. Patient demographic measures included within or derived from the EHR included sex, age at first OUD diagnosis, race, ethnicity, marital status and Geisinger Health Plan insurance coverage as of the date of consent for the larger study. Patients' age at first OUD diagnosis was categorized into the following age groups: 18–29, 30–39, 40–49, and 50 or older. Finally, the total length of care within the Geisinger Health System was calculated in years based on the first and last encounter dates within each record, along with the total number of encounters and number of encounters per year.

Analyses

First, years between first and last encounters, number of encounters per year, demographic characteristics, lifetime diagnoses for each condition, and lifetime dispensed buprenorphine and antidepressant medications were examined for the overall sample population, and separately for the OUD-only and co-occurring OUD and depression subgroups. Second, to identify differences in characteristics and comorbidities between the OUD-only and comorbid depression groups, multivariable logistic regression analyses, adjusting for age, sex, race, ethnicity, years between first and last EHR encounter and number of encounters per year were conducted. Confidence intervals were assessed at the 95% level and the measure of association was considered to be statistically significant at a level of $p < .05$. All analyses were conducted with Stata (version 14.2).

Results

Study sample characteristics

The analytic sample included 692 patients with at least one OUD diagnosis. Of these, 325 (47%) had at least one depression diagnosis in their lifetime. Sample characteristics are presented in Table 1, overall, and separately for OUD only and comorbid depression subgroups. In the total sample, 51.7% were male and over 70% were under the age of 40. Ninety-nine percent of the sample was white and 85.1% were not married. The mean number of years between the first and last Geisinger encounter across all patients was 11.7 years. The mean number of all outpatient, inpatient and emergency department encounters was 51.7, with an average of 8.1 encounters per year.

Differences between OUD with and without co-occurring depression

There were a number of differences between patients diagnosed with OUD with and without co-occurring depression (Table 1). Those with co-occurring OUD and depression were more likely to be female but did not differ on other demographic characteristics. Those with co-occurring depression had higher odds of having chronic pain conditions (aOR 2.54; 95% CI [1.75, 3.70]) and/or other medical conditions (aOR 1.94; 95% CI [1.37, 2.76]). Patients with co-occurring depression were also more likely to have other mental (aOR 7.05; 95% CI [4.73, 10.50]) and substance use disorders (aOR 4.95; 95% CI [2.82, 8.68]). Additionally, patients with co-occurring OUD and depression had higher odds of having at least one opioid overdose (aOR 3.81; 95% CI [2.04, 7.14]). Co-occurring depression was also associated with greater odds of at least one suicide attempt and/or ideation code (aOR 7.92; 95% CI [3.74, 16.78]). Finally, over 90% of all patients had at least one dispensed buprenorphine prescription, with no significant differences between those with and without co-occurring depression. Those with co-occurring depression were more likely to have received at least one dispensed antidepressant medication (aOR 6.05, 95% CI [3.92, 9.33]).

Discussion

In this sample of patients with OUD from a large integrated healthcare system, almost half also had a lifetime diagnosis of depression. Further, we found significant differences in other comorbidities and adverse health outcomes between patients with only OUD and those with co-occurring OUD and depressive disorders. Of particular concern, patients with lifetime comorbid depression had increased odds of lifetime opioid overdose. These patients also had increased odds of a suicide attempt or suicide ideation

code within their EHR. This is consistent with previous research indicating that psychiatric comorbidity is associated with an increased risk of non-fatal and fatal overdose (Campbell et al., 2018; Krawczyk et al., 2020), and suicide (Oquendo & Volkow, 2018).

Other medical conditions including hypertension, diabetes, COPD and asthma were more prevalent among people with a co-occurring depressive disorder. These comorbidities have been shown in populations of people with both OUD and depression separately, but have been explored less frequently among those who have co-occurring disorders. Results from the Australian Treatment Outcomes Study suggest that overall physical and mental health is worse among patients with heroin use disorder and comorbid depression than those without this comorbidity (Havard et al., 2006). Chronic pain is another significant comorbidity, and has been illustrated to be common among persons with OUD and depression (Higgins et al., 2020; Hser et al., 2017; Rosenblum et al., 2003). For example, a recent study assessed psychiatric comorbidity among treatment seeking individuals with OUD with and without chronic pain. The researchers found that compared to those without chronic pain, a higher proportion of those with chronic pain had increased anxiety and mood symptom severity, as well worse overall well-being (Higgins et al., 2020). Further, among people with non-cancer chronic pain, depression may moderate the relationship between increased pain severity and opioid use (Goesling et al., 2015). Lastly, high risk opioid analgesic prescribing practices including increased duration and dosage of prescriptions are associated with a greater risk of opioid overdose (Alexander et al., 2012; Dowell et al., 2016). The intersection between opioid use disorder, depression and other medical conditions including chronic pain has significant implications for understanding condition course, treatment plans and health outcomes. Research should continue to explore how to improve detection of these co-occurring conditions, as well as expand the evidence for most optimal treatment recommendations to decrease adverse health outcomes and improve overall well-being.

In regard to treatment, integrated care models exist to address the complex healthcare needs of people who have co-occurring disorders. Our results suggest that this population would benefit from highly-integrated services that meet their multiple needs. Integrated care creates the opportunity for greater provider coordination and could prevent frequent use of emergency and inpatient services, and improve patients' quality of life—opportunities that may be far less available in other health care settings where substance use treatment, mental health services, and other medical care are typically separate and far less integrated than in the Geisinger Healthcare System.

Limitations

This study used EHR data, which has many advantages including the capacity to assess real-world healthcare utilization. Another important advantage to highlight is the linkage between health records within the medication-based treatment programs and the rest of the health system, as this is not typical. Thus, this cohort offers a unique opportunity to examine comorbid conditions that may have been diagnosed in a range of health settings (including primary and specialty care) that are not typically associated with substance use treatment status. However, there are also a number of limitations to address. First, we rely on ICD codes for diagnoses and provider documentation of these codes, which could be influenced by practice styles, as well as insurance billing requirements. But, because of involvement in the prospective study, diagnoses of OUD were conferred by an addiction medicine clinician, except for one individual, who had a current diagnosis of alcohol use disorder but previous EHR diagnosis of OUD. Second, we were only able to assess characteristics and diagnostic codes included in the EHR; there are other health system-level and patient-level factors that could not be assessed. Third, it is possible that individuals received care from a non-Geisinger healthcare system, or could have died during the study period, which would not be captured in the EHR. Geisinger serves a population that has a very low outmigration rate (∼3–4%) and is the primary healthcare system within this area, so while there may be some missing data when seeking care from other providers, most data is represented in the primary service area (Carey et al., 2016). Another limitation of EHR data is that certain variables are not maintained longitudinally, including employment status, insurance status, marital status, etc.; we, therefore, were not able to explore these variables in a longitudinal manner. The time observed for each patient was not consistent and there is potential for ascertainment bias due to the nature of the data. To help account for this, we included length between the first and last visit and number of encounters per year in the adjusted models. Additionally, the sample includes almost exclusively white patients from rural Pennsylvania. This is consistent with Geisinger and

Pennsylvania's largely white population. Because of this, the results may not generalize to more racially diverse and urban populations. Finally, this sample is limited to patients who were seeking care within this health system. Therefore, the results might also be less generalizable to persons who may face greater barriers accessing care.

Conclusions

Opioid use and depressive disorders commonly co-occur. As we continue to develop policies and services to reduce the morbidity and mortality associated with the opioid epidemic, we should also be considering ways to address comorbid mental health disorders and depression in particular. This study highlights the comorbidities and adverse health outcomes of individuals with co-occurring opioid use and depression that are essential to consider when creating treatment plans and providing needed services.

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