Risk Factors and Outcomes of Opioid Users with and Without Concurrent Benzodiazepine Use in the North Carolina Medicaid Population

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ABSTRACT

BACKGROUND: Concurrent use of opioids and benzodiazepines is associated with increased risk of opioid overdose and death. Clinical guidelines recommend against this practice and quality measures incentivize plans to minimize concurrent use.

OBJECTIVE: To compare comorbidities, risky opioid-related behaviors such as high daily doses or multiple prescribers or pharmacies, and outcomes of users of opioids with and without benzodiazepine in the 2017-2018 North Carolina Medicaid population.

METHODS: This was a retrospective claims analysis that used 2017-2018 North Carolina Medicaid enrollment and administrative claims data to describe 3 populations: (1) opioid users who concurrently used benzodiazepine for at least 30 days, (2) opioid users who used some benzodiazepine for 0 to less than 30 overlapping days, and (3) opioid users who did not use benzodiazepines.

RESULTS: From 2017 to 2018, 6% of opioid users concurrently used opioids and benzodiazepines for at least 30 days, and 14% used some benzodiazepine for less than 30 overlapping days. Persons filling prescriptions for opioids and benzodiazepines were more likely to have mood disorders and more likely to have depression than opioid users who did not use benzodiazepines. Compared with those not using benzodiazepines, opioid users using benzodiazepine were also more likely to have higher daily opioid doses (at least 90 morphine milligram equivalents), at least 3 prescribers, and at least 3 pharmacies for opioid prescriptions. Although enrollees with at least 30 days of overlapping benzodiazepines and opioids had a higher percentage diagnosed with opioid use disorder compared with those with less than 30 days (30% vs. 13%), a similar percentage received medication-assisted treatment continuously for 90 days (2.6% vs. 2.7%) during 2017-2018. Users of opioids and benzodiazepines, whether for at least 30 overlapping days or less, had higher 1-year cumulative incidences of all-cause outpatient emergency department visits (64% and 65% vs. 52%) and all-cause hospitalizations (25% and 21% vs. 14%) compared with opioid users without benzodiazepine use.

CONCLUSIONS: Despite guidelines and quality measures, patients continue to use opioids and benzodiazepines concurrently. Addressing underlying mood disorders and depression, curbing risky opioid-related behaviors, and increasing access to medication-assisted treatment may benefit this population.

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What is already known about this subject

- Concurrent use of opioids and benzodiazepines is associated with increased risk of opioid overdose and death.
- In 2016, the Centers for Disease Control and Prevention (CDC) released guidelines advising clinicians to avoid prescribing opioids and benzodiazepines concurrently, and the U.S. Food and Drug Administration (FDA) added black box warnings to opioids and benzodiazepines regarding concurrent use.
- In 2018, a quality measure focusing on concurrent use of opioids and benzodiazepines for at least 30 days was added to the Medicaid Adult Core Set.

What this study adds

- During 2017-2018, 6% of the North Carolina Medicaid population used opioids and benzodiazepines for at least 30 overlapping days, and 14% used opioids and some benzodiazepine (0-29 overlapping days).
- Although current quality measures focus on the concurrent use of opioids and benzodiazepines for at least 30 overlapping days, this study shows that those who use opioids and some benzodiazepine (0-29 overlapping days) also have high rates of emergency department visits and hospitalizations.
- The differences in mental health comorbidities and risky opioid-related behaviors between concurrent and nonconcurrent user populations described in this study can help inform the design of potential clinical and utilization management programs as the North Carolina Medicaid program undergoes a transformation from fee for service to managed care.

The concurrent use of an opioid and a benzodiazepine increases risk of opioid overdose, emergency department visits, inpatient admissions, and death.¹⁻⁶ This increase of risk is likely because of the increased risk of respiratory depression when opioids are used with benzodiazepines.⁷ In March 2016, the Centers for Disease Control and Prevention (CDC) advised clinicians to avoid prescribing opioids and benzodiazepines concurrently whenever possible as part of its "Guideline for Prescribing Opioids for Chronic Pain."^{7,8} In August 2016, the U.S. Food and Drug Administration (FDA) added black box warnings to all drugs in the opioid and

benzodiazepine drug classes. In 2018, a measure developed by the Pharmacy Quality Alliance (PQA) depicting concurrent use of an opioid and a benzodiazepine for at least 30 days was added to the Medicaid Adult Core Set, which is a set of health care quality measures for adult Medicaid enrollees, as well as the Medicaid 1115 Substance Use Disorder Demonstrations.

Despite these policy and reporting recommendations, the concurrent use of opioids and benzodiazepines continues to occur. What remains unknown is how concurrent users differ from those using opioids alone in terms of demographics and comorbidities and whether they exhibit risky opioid-related behaviors, such as receipt of high doses of opioids and opioids from multiple prescribers and/or pharmacies. The results of this study will help providers and payers design programs and initiatives to address this risky population.

Methods

We used 2017-2018 North Carolina (NC) Medicaid enrollment and claims data to identify enrollees who filled at least 1 opioid prescription. Due to data access limitations, we excluded those enrollees aged over 65 years or who had Medicare dual eligibility. We required enrollment at the cohort index date and for each prescription that was analyzed. We identified all prescriptions for opioids and benzodiazepines using National Drug Code numbers linked to the CDC's morphine milligram equivalents (MME) table.⁹ We then subdivided this population into 3 mutually exclusive comparison groups: (1) those who continuously used an opioid and a benzodiazepine with at least 30 days of overlap (modeled after the PQA measure¹⁰); (2) those who used an opioid and some benzodiazepines (but with 0 to less than 30 days of overlap); and (3) those who used an opioid but did not use a benzodiazepine.

Baseline demographics, selected diagnosed comorbidities, prescription opioid-related characteristics, receipt of medication-assisted treatment, and 1-year outcomes were compared between the 3 groups. Demographics included age, sex, and race/ethnicity, along with Medicaid eligibility category, managed care region, and residence type. The 6 managed care regions represented the proposed regions in NC's Medicaid transformation.¹¹ Selected diagnosed comorbidities included mood disorders, depression, schizophrenia, any cancer, and chronic pain and were identified based on at least 1 prespecified *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code (see Appendix A and Appendix B, available in online article). Similar to past studies that evaluated opioid and benzodiazepine use, mental health comorbidities were reported.^{1,6,12} Cancer and chronic pain were selected because higher doses and longer durations of opioid use are often seen for these indications.

Prescription opioid-related characteristics per enrollee included receipt of at least 90 daily MME; receipt of at least a continuous 90-day supply of 90 daily MME; use of at

least 3 prescribers; use of at least 3 pharmacies; and use of at least 4 prescribers and at least 4 pharmacies to fill opioid prescriptions at any point in 2017-2018. Comorbidities were identified using the 90 days before the index date for each group, with index dates defined as the 30th day of continuous opioid and benzodiazepine overlap for cohort 1 and first date of opioid prescription for cohorts 2 and 3.

Medication-assisted treatment included prescriptions for the tablet and film formulations of generic buprenorphine or buprenorphine and naloxone in combination. One-year outcomes included all-cause mortality, all-cause hospitalization, outpatient emergency department (ED) visit, and diagnosis of an unintentional opioid overdose. These outcomes were derived from at least 1 prespecified Healthcare Common Procedure Coding System and/or ICD-10-CM code (see Appendix A).

Statistical Analysis

Baseline demographic and prescription opioid characteristics were described using frequencies with percentages for categorical variables and means with standard deviations for continuous variables. Chi-square and Kruskal-Wallis tests were used to test for differences across groups for categorical and continuous variables, respectively.

One-year cumulative incidence of all-cause mortality was calculated via the Kaplan-Meier function. One-year cumulative incidence of all-cause hospitalization, outpatient ED visit, and unintentional opioid overdose were calculated using the cumulative incidence function, accounting for the competing risk of death.¹³ For all-cause mortality, enrollees were censored at the earliest of the end of their Medicaid enrollment, the end of the period, or 1 year from their cohort index date. All other outcomes were additionally censored for mortality.

We tested for group differences in mortality using log-rank tests and for all other outcomes using Gray tests.¹⁴ A *P* value of less than 0.05 was considered statistically significant for all tests. All analyses were performed at the patient level and were done using SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the Duke University Health System Institutional Review Board.

Results

From 2017 to 2018, there were 2,823,633 enrollees in NC Medicaid. As shown in Figure 1, there were 2,457,174 persons aged under 65 years in NC who were enrolled in Medicaid and who were not dual eligible for Medicare. Of these, 322,835 (13%) filled at least 1 opioid prescription. Of these opioid users, 18,197 (6%) had concurrent opioid and benzodiazepine prescriptions that overlapped for at least 30 days; 45,242 (14%) had prescriptions for an opioid and a benzodiazepine with 0-29 days of overlap; and the majority (80%) did not have benzodiazepine use (Table 1).

FIGURE 1 Patient Selection Flowchart

NC = North Carolina.

Differences in Patient Characteristics and Comorbidities

Compared with opioid users with no benzodiazepine use, opioid users with at least 30 days and opioid users with less than 30 days of overlapping benzodiazepines were older (mean age of 47 and 36 years vs. 30 years), more likely to be white (75% and 67% vs. 48%), and more likely to qualify for Medicaid based on disability (63% and 36% vs. 23%). Those with concurrent use for at least 30 days and those with at least some benzodiazepine use also had higher percentages with diagnosed mental health-related comorbidities compared with opioid users with no benzodiazepine use (mood disorder: 41% and 29% vs. 11%; depression: 40% and 28% vs. 12%; schizophrenia: 5% and 4% vs. 1%, respectively). All differences were statistically significant.

Differences in Opioid Prescription Characteristics and Medication-Assisted Treatment

Opioid users with at least 30 days of overlapping benzodiazepines and opioid users with some benzodiazepine use were more likely to fill a prescription with at least 90 daily MME in 2017-2018 (32% and 15% vs. 6%) compared with those with no benzodiazepine use. Moreover, opioid users with at least 30 days of overlapping benzodiazepines and opioid users with some benzodiazepine use were more likely to have filled opioid prescriptions from at least 3 prescribers or at least 3 pharmacies compared with opioid users with no benzodiazepine use (at least 3 prescribers: 49% and 24% vs. 12%, respectively; at least 3 pharmacies: 24% and 9% vs. 4%, respectively).

Although enrollees with at least 30 days of overlapping benzodiazepines and opioids had a higher percentage diagnosed with opioid use disorder compared with those with less than 30 days overlap (30% vs. 13%; Table 2), similar percentages received medication-assisted treatment at all (4.4% versus 4%) or continuously for 90 days (2.6% versus 2.7%) at any point in 2017-2018. Meanwhile, 9% of opioid users with no benzodiazepine use were diagnosed with opioid use disorder, and 2.1% and 1.4% received medication-assisted treatment at all or continuously for 90 days, respectively.

Differences in Outcomes

Opioid users with at least 30 days of overlapping benzodiazepines and opioid users with some benzodiazepine use had higher 1-year cumulative incidences of outpatient ED visits (64% and 65% vs. 52%; Table 2) and hospitalizations (25% and 21% vs. 14%) compared with opioid users without benzodiazepine use. One-year cumulative incidences of all-cause mortality (4% and 2% vs. 1%, respectively) and unintentional opioid overdose (1.1% and 0.4% vs. 0.2%, respectively) were higher for opioid users with at least 30 days of overlapping benzodiazepines and opioid users with some benzodiazepine use versus opioid users with no benzodiazepine use.

Discussion

In a cohort of NC Medicaid enrollees in 2017-2018, we found that 6% of opioid users concurrently used a benzodiazepine

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TABLE 1 Demographics and Comorbidities of NC Medicaid Opioid Users with and Without Benzodiazepine Use

	Total Any Opioid Use	Subgroup 1 Overlapping Benzodiazepine and Opioid Use for ≥ 30 Days	Subgroup 2 Opioid and Some Benzodiazepine Use	Subgroup 3 Opioid Use But No Benzodiazepine Use	P Value ^a
Number	322,835	18,197	45,242	259,396	
Demographics					
Age, mean (SD)	31.6 (15.6)	47.2 (10.6)	36.2 (14.7)	29.7 (15.3)	<0.001
Male sex, n (%)	100,832 (31.2)	5,267 (28.9)	11,493 (25.4)	84,072 (32.4)	<0.001
Race, n (%)					
African American	115,821 (35.9)	2,906 (16.0)	10,622 (23.5)	102,293 (39.4)	<0.001
White	168,011 (52.0)	13,592 (74.7)	30,182 (66.7)	124,237 (47.9)	<0.001
Other race	39,003 (12.1)	1,699 (9.3)	4,438 (9.8)	32,866 (12.7)	<0.001
Medicaid eligibility n (%)					
Average days of enrollment, mean (SD)	428.0 (225.6)	532.1 (196.5)	461.1 (215.3)	408.6 (223.7)	<0.001
Aid to families	172,744 (53.5)	6,254 (34.4)	24,126 (53.3)	142,275 (54.8)	<0.001
Aid to children	41,425 (12.8)	20 (0.1)	3,240 (7.2)	38,165 (14.7)	<0.001
Aid to disabled	86,429 (26.8)	11,431 (62.8)	16,280 (36.0)	58,802 (22.7)	<0.001
Medicaid for pregnant women	17,301 (5.4)	15 (0.1)	665 (1.5)	16,610 (6.4)	<0.001
Refugee medical assistance	158 (0.0)	–	–	155 (0.1)	<0.001
Other	4,778 (1.5)	477 (2.6)	928 (2.1)	3,389 (1.3)	<0.001
Managed care region, n (%)					
Region 1 (West, Asheville)	33,787 (10.5)	2,594 (14.3)	7,566 (16.7)	23,624 (9.1)	<0.001
Region 2 (Northwest)	54,814 (17.0)	3,751 (20.6)	6,819 (15.1)	44,240 (17.1)	<0.001
Region 3 (Southwest, Mecklenburg)	72,436 (22.4)	3,843 (21.1)	11,276 (24.9)	57,324 (22.1)	<0.001
Region 4 (North, Durham/Wake)	53,548 (16.6)	2,032 (11.2)	6,507 (14.4)	45,004 (17.3)	<0.001
Region 5 (South)	63,901 (19.8)	3,631 (20.0)	7,125 (15.7)	53,152 (20.5)	<0.001
Region 6 (East, Coastal)	44,246 (13.7)	2,343 (12.9)	5,934 (13.1)	35,969 (13.9)	<0.001
Residence, n (%)					
Private living arrangement	316,644 (98.1)	17,445 (95.9)	43,879 (97.0)	255,313 (98.4)	<0.001
In SNF or domiciliary care	2,088 (0.6)	416 (2.3)	543 (1.2)	1,134 (0.4)	<0.001
In foster care or adoption home	2,204 (0.7)	–	218 (0.5)	1,985 (0.8)	<0.001
Other living arrangement	1,899 (0.6)	335 (1.8)	602 (1.3)	964 (0.4)	<0.001
Medical history, n (%)					
Mood disorders	48,586 (15.0)	7,473 (41.1)	12,954 (28.6)	28,747 (11.1)	<0.001
Depression	49,500 (15.3)	7,209 (39.6)	12,850 (28.4)	30,077 (11.6)	<0.001
Schizophrenia	6,375 (2.0)	880 (4.8)	1,865 (4.1)	3,671 (1.4)	<0.001
Any cancer	9,026 (2.8)	1,337 (7.3)	2,061 (4.6)	5,763 (2.2)	<0.001
Chronic pain	121,931 (37.8)	15,265 (83.9)	21,472 (47.5)	85,864 (33.1)	<0.001

Note: Cells with dashes indicate that small cell sizes (<11) have been suppressed.

^aHypothesis testing excluded the “any opioid Rx” group.

NC = North Carolina; Rx = prescription; SD = standard deviation; SNF = skilled nursing facility.

for at least 30 days, and an additional 14% had some use of benzodiazepine for 0-29 days of overlap. A past study found that in 2015, 28% of opioid users in the Pennsylvania Medicaid population concurrently used benzodiazepines for at least 30 days.¹² However, study authors excluded those aged <18 or >64 years, those with cancer, and those dual eligible for Medicare and Medicaid, and focused on patients more likely to have chronic as opposed to acute pain, per the PQA quality measure.¹² In comparison, our study included patients aged <65 years and those with cancer. Another study in the Georgia Medicaid population found that in 2014, 10%-15% of opioid

users had concurrent opioid and benzodiazepine use for at least 7 days.¹⁵ Across a commercial population, approximately 17% of opioid users in 2013 also concurrently used benzodiazepines for at least 1 day.⁶ To our knowledge, our study is the first to describe the population that concurrently used opioids and benzodiazepines in a Medicaid population after the CDC and FDA recommendations in 2016.

Despite the lower percentage of concurrent use of opioids and benzodiazepines for at least 30 days, this continues to be an important population to monitor because of the multiple comorbidities and risky opioid-related behaviors, such as high

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TABLE 2 Opioid Prescription Characteristics, Medication-Assisted Treatment, and Outcomes of NC Medicaid Opioid Users with and Without Benzodiazepine Use

	Total Any Opioid Use	Subgroup 1 Overlapping Benzodiazepine and Opioid Use for ≥ 30 Days	Subgroup 2 Opioid and Some Benzodiazepine Use	Subgroup 3 Opioid use But No Benzodiazepine Use	P Value ^a
Opioid prescription characteristics, n (%)					
At least 90 MME	27,820 (8.6)	5,848 (32.1)	6,575 (14.5)	15,397 (5.9)	<0.001
At least 90 days supply of 90 MME	10,211 (3.2)	4,492 (24.7)	1,010 (2.2)	4,709 (1.8)	<0.001
At least 3 prescribers	51,189 (15.9)	8,981 (49.4)	11,025 (24.4)	31,183 (12.0)	<0.001
At least 3 pharmacies	19,536 (6.1)	4,445 (24.4)	3,995 (8.8)	11,096 (4.3)	<0.001
At least 4 prescribers + 4 pharmacies	3,782 (1.2)	846 (4.6)	918 (2.0)	2,018 (0.8)	<0.001
Opioid or substance use disorder and MAT, n (%)					
Diagnosed with OUD	28,921 (9.0)	5,446 (29.9)	6,004 (13.3)	17,471 (6.7)	<0.001
Diagnosed with SUD	48,424 (15.0)	7,621 (41.9)	9,770 (21.6)	31,033 (12.0)	<0.001
Received MAT	6,892 (2.1)	803 (4.4)	1,814 (4.0)	4,275 (1.6)	<0.001
Continuously received 90 days of MAT	4,491 (1.4)	470 (2.6)	1,232 (2.7)	2,789 (1.1)	<0.001
Cumulative incidence of outcomes, % (95% CI)					
All-cause mortality	1.4 (1.4-1.5)	4.3 (4.0-4.6)	2.2 (2.1-2.4)	1.1 (1.1-1.2)	<0.001
All-cause hospitalization	15.6 (15.5-15.7)	25.1 (24.4-25.7)	21.4 (21.0-21.9)	13.6 (13.5-13.8)	<0.001
Outpatient ED visit	54.4 (54.2-54.6)	63.9 (63.1-64.6)	64.7 (64.2-65.1)	51.5 (51.3-51.8)	<0.001
Unintentional opioid overdose	0.3 (0.2-0.3)	1.1 (1.0-1.3)	0.4 (0.3-0.4)	0.2 (0.1-0.2)	<0.001

Note: All analyses are at the patient level.

^aHypothesis testing excluded the “any opioid Rx” group.

CI=confidence interval; ED=emergency department; MAT=medication-assisted treatment; MME=morphine milligram equivalents; OUD=opioid use disorder; Rx=prescription; SUD=substance use disorder.

doses and multiple prescribers and pharmacies. In this study, approximately 40% of those who concurrently used an opioid and a benzodiazepine for at least 30 days had mood disorders compared with only 11% of opioid users who did not use benzodiazepines. Similar percentages were seen for depression. These results are similar to findings from other state Medicaid programs (60% of the concurrent user population had mood disorders) and greater than what has been reported in commercial populations (17% of the concurrent user population had depression).^{6,12}

Previous Medicaid studies have found that the concurrent use of opioids and benzodiazepines occurs most frequently out of all the potential opioid misuse measures, such as high doses, multiple prescribers, overlapping opioid prescriptions, and long-acting opioids for acute pain.^{12,15} Given that benzodiazepines are approved by the FDA for anxiety disorders, among several indications, and that Medicaid is the single largest payer for mental health services in the United States,¹⁶ the concurrent use of opioids and benzodiazepines will require special attention in Medicaid populations, unless the underlying mental health comorbidities in the population are reduced through appropriate treatment. Starting October 2019, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act will require state Medicaid programs to monitor the concurrent use

of opioids and benzodiazepines. Future research should evaluate whether this monitoring requirement reduces concurrent use in Medicaid populations.

In addition, the concurrent user group tended to have higher rates of risky opioid-related behaviors, such as prescriptions for high opioid doses and multiple prescribers and pharmacies, both of which are considered inappropriate and monitored by quality measures.¹⁰ Nearly one third of those who concurrently used an opioid and a benzodiazepine for at least 30 days also had at least 1 prescription with an average daily MME of at least 90. Also, approximately one quarter had at least a continuous 90-day supply of 90 daily MME. Moreover, almost one half of concurrent users filled opioids from at least 3 different prescribers, and almost one quarter of concurrent users filled opioids from at least 3 pharmacies. Although the current PQA measure for multiple prescribers and pharmacies requires at least 4 prescribers and 4 pharmacies, evidence suggests that the use of at least 3 prescribers or at least 3 pharmacies is associated with increased opioid overdose and mortality.¹⁷ Designing utilization management programs to restrict patients from using high doses of opioids and multiple sources of prescribers or pharmacies for opioid prescriptions may be needed, especially in this population.

Although concurrent users of opioids and benzodiazepines for at least 30 days had more than twice the rate of opioid use

disorder diagnosis compared with concurrent users of opioid and benzodiazepine for less than 30 days, rates of medication-assisted treatment were similar. This could indicate a gap in the use of medication-assisted treatment for health plans to address, especially as Medicaid increasingly plays a larger role in the reimbursement of substance use disorder services.¹⁶

Currently, the PQA quality measure in use for Medicaid populations (and endorsed by the National Quality Forum) focuses on the concurrent use of opioids and benzodiazepines for at least 30 days. However, this study found that concurrent users of opioids and benzodiazepines for at least 30 days, as well as opioid users who used some but less than 30 days of overlapping benzodiazepines, had high levels of ED visits and hospitalizations. A past study suggested that the elimination of the concurrent use of even 1 day of overlapping opioids and benzodiazepines could reduce the risk of ED visits and hospitalizations for opioid overdose by an estimated 15%.⁶ Considering the high costs associated with ED visits and hospitalizations, it would be important for a health plan to monitor concurrent users of an opioid and a benzodiazepine for at least 30 days of overlap, as well as any overlap.

As NC Medicaid shifts from fee for service to managed care, health plans have an opportunity to decrease inappropriate opioid use, benzodiazepine use, and concurrent opioid and benzodiazepine use. A past study suggested that compared with fee for service, managed care Medicaid could be more effective at reducing inappropriate opioid prescribing.¹⁵ However, this is 1 study, and future research should evaluate whether pharmacy program management in fee-for-service versus managed care environments perform better at reducing inappropriate opioid use. At the least, health plans being held accountable to quality measures will want to understand their concurrent opioid and benzodiazepine user populations.

Limitations

This study examined Medicaid enrollees in NC, but findings may not apply beyond this population. Nevertheless, NC Medicaid's current transformation from fee for service to managed care makes this study population timely and relevant to these managed care plans. In addition, we did not require a full year of Medicaid eligibility to be included in the study; therefore, we may be missing enrollees who had overlapping benzodiazepine and opioid prescriptions for at least 30 days outside of their eligibility period. However, the average number of days of Medicaid enrollment was greater than 365.

Since this study used only enrollment and claims data, actual medication consumption may differ from the prescriptions filled. For example, medications paid for by cash were not captured in the claims data. Also, since unintentional opioid overdoses were measured based on ICD-10-CM codes, overdoses could be underestimated if some overdoses were rescued before medical care was sought. Finally, this is a descriptive study and does not evaluate causality.

Conclusions

Concurrent users of opioids and benzodiazepines can have more mental health comorbidities; higher prescription opioid doses; multiple prescription opioid prescribers and pharmacies; disproportionately lower medication-assisted treatment; and higher cumulative incidences of opioid overdose, ED visits, hospitalizations, and death than those using opioids alone. Providers and payers should address underlying mental health issues, curb risky opioid-related behaviors, and increase access to medication-assisted treatment.

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APPENDIX A Outcomes and How They Were Measured

Outcome	Measurement Definition
All-cause mortality	Death date
All-cause hospitalization	Date of inpatient encounter from an institutional claim
All-cause outpatient ED visit	Date of ED visit from institutional encounter with HCPCS code 9928x or professional encounter with revenue code 0981 or 045x
Unintentional opioid overdose	At least 1 institutional or professional claim with an ICD-10-CM code as noted in Appendix B

ED=emergency department; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification.

APPENDIX B ICD-10-CM Diagnosis Codes

Diagnosis	ICD-10-CM
Substance use disorder (SUD) ¹	F10.10, F10.11, F10.120, F10.121, F10.129, F10.14, F10.150, F10.151, F10.159, F10.180, F10.181, F10.182, F10.188, F10.19, F10.20, F10.21, F10.220, F10.221, F10.229, F10.230, F10.231, F10.232, F10.239, F10.24, F10.250, F10.251, F10.259, F10.26, F10.27, F10.280, F10.281, F10.282, F10.288, F10.29, F10.920, F10.921, F10.929, F10.94, F10.950, F10.951, F10.959, F10.96, F10.97, F10.980, F10.981, F10.982, F10.988, F10.99, F11.10, F11.11, F11.120, F11.121, F11.122, F11.129, F11.14, F11.150, F11.151, F11.159, F11.181, F11.182, F11.188, F11.19, F11.20, F11.21, F11.220, F11.221, F11.222, F11.229, F11.23, F11.24, F11.250, F11.251, F11.259, F11.281, F11.282, F11.288, F11.29, F11.90, F11.920, F11.921, F11.922, F11.929, F11.93, F11.94, F11.950, F11.951, F11.959, F11.981, F11.982, F11.988, F11.99, F12.10, F12.11, F12.120, F12.121, F12.122, F12.129, F12.150, F12.151, F12.159, F12.180, F12.188, F12.19, F12.20, F12.21, F12.220, F12.221, F12.222, F12.229, F12.250, F12.251, F12.259, F12.280, F12.288, F12.29, F12.90, F12.920, F12.921, F12.922, F12.929, F12.950, F12.951, F12.959, F12.980, F12.988, F12.99, F13.10, F13.11, F13.120, F13.121, F13.129, F13.14, F13.150, F13.151, F13.159, F13.180, F13.181, F13.182, F13.188, F13.19, F13.20, F13.21, F13.220, F13.221, F13.229, F13.230, F13.231, F13.232, F13.239, F13.24, F13.250, F13.251, F13.259, F13.26, F13.27, F13.280, F13.281, F13.282, F13.288, F13.29, F13.90, F13.920, F13.921, F13.929, F13.930, F13.931, F13.932, F13.939, F13.94, F13.950, F13.951, F13.959, F13.96, F13.97, F13.980, F13.981, F13.982, F13.988, F13.99, F14.10, F14.11, F14.120, F14.121, F14.122, F14.129, F14.14, F14.150, F14.151, F14.159, F14.180, F14.181, F14.182, F14.188, F14.19, F14.20, F14.21, F14.220, F14.221, F14.222, F14.229, F14.23, F14.24, F14.250, F14.251, F14.259, F14.280, F14.281, F14.282, F14.288, F14.29, F14.90, F14.920, F14.921, F14.922, F14.929, F14.94, F14.950, F14.951, F14.959, F14.980, F14.981, F14.982, F14.988, F14.99, F15.10, F15.11, F15.120, F15.121, F15.122, F15.129, F15.14, F15.150, F15.151, F15.159, F15.180, F15.181, F15.182, F15.188, F15.19, F15.20, F15.21, F15.220, F15.221, F15.222, F15.229, F15.23, F15.24, F15.250, F15.251, F15.259, F15.280, F15.281, F15.282, F15.288, F15.29, F15.90, F15.920, F15.921, F15.922, F15.929, F15.93, F15.94, F15.950, F15.951, F15.959, F15.980, F15.981, F15.982, F15.988, F15.99, F16.10, F16.11, F16.120, F16.121, F16.122, F16.129, F16.14, F16.150, F16.151, F16.159, F16.180, F16.183, F16.188, F16.19, F16.20, F16.21, F16.220, F16.221, F16.229, F16.24, F16.250, F16.251, F16.259, F16.280, F16.283, F16.288, F16.29, F16.90, F16.920, F16.921, F16.929, F16.94, F16.950, F16.951, F16.959, F16.980, F16.983, F16.988, F16.99, F17.203, F17.208, F17.209, F17.213, F17.218, F17.219, F17.223, F17.228, F17.229, F17.293, F17.298, F17.299, F18.10, F18.11, F18.120, F18.121, F18.129, F18.14, F18.150, F18.151, F18.159, F18.17, F18.180, F18.188, F18.19, F18.20, F18.21, F18.220, F18.221, F18.229, F18.24, F18.250, F18.251, F18.259, F18.27, F18.280, F18.288, F18.29, F18.90, F18.920, F18.921, F18.929, F18.94, F18.950, F18.951, F18.959, F18.97, F18.980, F18.988, F18.99, F19.10, F19.11, F19.121, F19.122, F19.129, F19.14, F19.150, F19.151, F19.159, F19.16, F19.17, F19.180, F19.181, F19.182, F19.188, F19.19, F19.20, F19.21, F19.220, F19.221, F19.222, F19.229, F19.230, F19.231, F19.232, F19.239, F19.24, F19.250, F19.251, F19.259, F19.26, F19.27, F19.280, F19.281, F19.282, F19.288, F19.29, F19.920, F19.921, F19.922, F19.929, F19.930, F19.931, F19.932, F19.939, F19.94, F19.950, F19.951, F19.959, F19.96, F19.97, F19.980, F19.981, F19.982, F19.988, F19.99, F55.0, F55.1, F55.2, F55.3, F55.4, F55.8, G62.1, I42.6, K29.20, K70.0, K70.10, K70.11, K70.2, K70.30, K70.31, K70.40, K70.41, K70.9, O99.320, O99.321, O99.322, O99.323, O99.324, O99.325, T40.0X1A, T40.0X2A, T40.0X3A, T40.0X4A, T40.0X5A, T40.0X5S, T40.1X1A, T40.1X2A, T40.1X3A, T40.1X4A, T40.2X1A, T40.2X2A, T40.2X3A, T40.2X4A, T40.3X1A, T40.3X2A, T40.3X3A, T40.3X4A, T40.4X1A, T40.4X2A, T40.4X3A, T40.4X4A, T40.601A, T40.602A, T40.603A, T40.604A, T40.691A, T40.692A, T40.693A, T40.694A, T40.694A, T40.7X1A, T40.7X2A, T40.7X3A, T40.7X4A, T40.7X5A, T40.7X5S, T40.8X1A, T40.8X2A, T40.8X3A, T40.8X4A, T40.901A, T40.902A, T40.903A, T40.904A, T40.905A, T40.905S, T40.991A, T40.992A, T40.993A, T40.994A, T40.995A, T40.995S, T41.3X1A, T41.3X2A, T41.3X3A, T41.3X4A
Opioid use disorder (OUD) ^{2,3}	F11.10, F11.11, F11.120, F11.129, F11.20, F11.21, F11.220, F11.221, F11.222, F11.229, F11.23, F11.24, F11.250, F11.251, F11.259, F11.281, F11.282, F11.288, F11.29, F11.90
Unintentional opioid overdose	T40.0X1A, T40.2X1A, T40.3X1A, T40.4X1A, T40.601A, T40.691A
Nonmetastatic and metastatic cancers ⁴	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.0x-C45.2x, C45.7x, C45.9x, C46.x-C48.x, C72.x-C86.x, C88.2x-C88.4x, C88.8x, C88.9x, C90.x-C93.x, C94.1x-C94.3x, C94.8x, C95.x, C96.0x, C96.2x, C96.4x, C96.9x, C96.Ax, C96.Zx, D03.x, D45.x, D47.Z9 in any position

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APPENDIX B ICD-10-CM Diagnosis Codes (continued)

Diagnosis	ICD-10-CM
Chronic pain ⁵	F45.41, F45.42, G44.209, G89.0*, G89.21, G89.22, G89.28, G89.29, G89.4*, M25.50, M25.51, M25.55-M25.57, M25.78, M43.2*, M43.6*, M43.8*9, M46.1*, M46.41-M46.47, M46.9*, M47.0*, M47.02, M47.1*, M47.24-M47.28, M47.814, M47.815, M47.816, M47.817, M47.818, M47.894-M47.898, M48.04-M48.08, M48.1*, M48.9*, M50.0*, M50.1*, M50.3*, M50.8*, M50.9*, M51.04-M51.06, M51.1*, M51.24, M51.25, M51.3*, M51.4*, M51.8*, M51.9*, M53.1*, M53.2*7, M53.2*8, M53.3*, M53.8*, M53.9*, M54.*, M60.8*, M60.9*, M62.830, M67.88, M72.9*, M79.1*, M79.2*, M79.6*, M79.7*, M96.1*, M99.22-M99.29, M99.32-M99.39, M99.42-M99.49, M99.52-M99.59, M99.62-M99.69, M99.72-M99.79
HIV ⁶	B20, B97.35, D84.8, R75, R97.0, or R97.1 in any position
Schizophrenia and other psychotic disorders ⁷	F20.x, F21, F22, F23, F24, F25.x, F28, F29, F06.0, F06.2 in any position
Mood disorders (i.e. bipolar, manic depression, etc.) ⁷	F30.x, F31.x, F32.x, F33.x, F34.x, F39, F06.3x, R45.86 in any position
Depression ⁴	F31.3x, F31.4x, F31.5x, F31.75, F31.76, F32.x, F33.x, F34.1x, F43.10, F42.11, F43.12, F43.2x, F43.8x, F43.9x, F93.0x, F94.8x in any position

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