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# Sedative-hypnotic Co-prescribing with Opioids in a Large Network of Community Health Centers

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## Abstract

**Objective:** When prescribed with opioids, sedative-hypnotics substantially increase the risk of overdose. The objective of this paper was to describe characteristics and trends in opioid sedative-hypnotic co-prescribing in a network of safety-net clinics serving low-income, publicly insured, and uninsured individuals. **Methods:** This retrospective longitudinal analysis of prescription orders examined opioid sedative-hypnotic co-prescribing rates between 2009 and 2018 in the OCHIN network of safety-net community health centers. Sedative-hypnotics included benzodiazepine and non-benzodiazepine sedatives (eg, zolpidem). Co-prescribing patterns were assessed overall and across patient demographic and co-morbidity characteristics. **Results:** From 2009 to 2018, 240 587 patients had ≥1 opioid prescriptions. Most were White (65%), female (59%), and had Medicaid insurance (43%). One in 4 were chronic opioid users (25%). During this period, 55 332 (23%) were co-prescribed a sedative-hypnotic. The prevalence of co-prescribing was highest for females (26% vs 19% for males), non-Hispanic Whites (28% vs 13% for Hispanic to 20% for unknown), those over 44 years of age (25% vs 20% for <44 years), Medicare insurance (30% vs 21% for uninsured to 22% for other/unknown), and among those on chronic opioid therapy (40%). Co-prescribing peaked in 2010 (32%) and declined steadily through 2018 (20%). Trends were similar across demographic subgroups. Co-prescribed sedative-hypnotics remained elevated for those with chronic opioid use (27%), non-Hispanic Whites (24%), females (23%), and those with Medicare (23%) or commercial insurance (22%). **Conclusions:** Co-prescribed sedative-hypnotic use has declined steadily since 2010 across all demographic subgroups in the OCHIN population. Concurrent use remains elevated in several population subgroups.

## Keywords

opioids, benzodiazepines, sedative-hypnotics

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## Background

When combined with opioids, benzodiazepines, and other central nervous system depressants greatly potentiate the risk for overdose. Epidemiologic studies find that when combined with an opioid, benzodiazepines increase the risk of overdose by 2 to 5 fold.[1-3] In 2020, over 12 000 individuals died of an overdose that involved a benzodiazepine.[4] A large majority (86%) of these fatalities also involved opioids. Despite these risks, co-prescribing remains relatively common. Between 2002 and 2014, the proportion of individuals receiving combined opioid and benzodiazepine prescriptions increased 40%.[5] Recent studies indicate 1 in 5 outpatient visits where an opioid was prescribed also involved a co-prescribed benzodiazepine.[6]

Federal health authorities have taken steps to mitigate risks associated with co-prescribed benzodiazepines on several fronts. In March 2016, the Centers for Disease Control and Prevention (CDC) issued their Guidelines for

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Prescribing Opioids for Chronic Pain which highlighted the risks of co-administration of benzodiazepines and opioids.[7] Later that year (August), the US Food and Drug Administration (FDA) added boxed warnings to the labeling of benzodiazepines and opioids about the hazards of combining these medications. Two longitudinal studies using large nationally representative dispensing data have evaluated changes in opioid and benzodiazepine co-prescribing following the CDC guideline and FDA labeling changes. An evaluation by Bohnert et al[8] found that release of the CDC prescribing guidelines was associated with a small (0.06% per month reduction) decline in the trend of patients with overlapping benzodiazepines and opioids. Further analysis of the same dataset found that rates of co-prescribing declined nearly 18% following the FDA's strengthening of the label warning.[9] Another study of individuals with commercial insurance or Medicare Advantage found modest declines among individuals on long-term opioid therapy but little change in those on short-term therapy.[10]

We have previously reported early and rapid declines in opioid prescribing among patients receiving care in a large network of safety-net community health centers.[11] Trends in co-prescribed benzodiazepines and other sedative-hypnotics in this population are not known. The objective of this study was to characterize trends in co-prescription of opioids and sedative hypnotics in a large network of community health centers.

## Methods

### Data Sources and Study Population

In this serial cross-sectional study, we used electronic health record (EHR) data from the OCHIN ambulatory care clinic data repository. OCHIN, the largest network of community healthcare clinics in the country, is comprised of 1005 safety-net clinics in 21 states that provide care to individuals regardless of insurance status. OCHIN clinics include Federally Qualified Health Centers, county health departments, and not-for-profit clinics all sharing a common EHR platform (Epic©, Epic Systems Corporation).

Adult patients over 18 years of age were included if they had one or more primary care visits to an OCHIN clinic and had at least one opioid analgesic prescription order at any point during the study period (January 2009-December 2018). Patient age was calculated from the date for their first opioid prescription. For included patients, we created 20 six-month cross-sectional measures of medication orders to assess the potential for opioid and sedative-hypnotic co-prescribing. The first and last periods were excluded from analyses to allow equal intervals for co-prescription (either 6 months before or 6 months after the initial prescription).

### Variable Definitions

As previously described, prescription orders in EHR records include variables that identify the generic name, form, strength, quantity, and pharmaceutical class.[11] Opioids included all opioids that can be prescribed on an outpatient basis for analgesia and excluded those classified as expectorants, antitussives, or antidiarrheal. We also excluded formulations of buprenorphine that are indicated for opioid use disorder. Our primary outcome was sedative-hypnotic and opioid co-prescribing. This was defined as a sedative-hypnotic order placed in the same 6-month calendar period as any opioid order. Sedative-hypnotic medications included both benzodiazepines and non-benzodiazepine sedatives such as zolpidem. EHR Medication order data only includes information on the original prescription order and the number of refills and does not have information about if and when those refills were dispensed. We considered new opioid and sedative-hypnotic prescription orders entered in the same 6-month period to be conservative estimation of concurrent use.

### Analyses

For each cross-sectional 6-month period, we determined proportion of patients for whom an opioid was ordered and who also were co-prescribed a sedative-hypnotic during that period. Among these individuals, we characterized their demographics and specific mental health co-morbidities. Demographic factors included gender, race and ethnicity, age (19-44, 45-64, >64), and medical insurance type. Co-morbidities were identified from the patient's problem list occurring at any point in the study period and included anxiety, depression, sleep disorder, seizure disorder, alcohol use disorder, opioid use disorder, and other (non-alcohol/opioid) substance use disorders. We also identified patients with chronic opioid therapy defined as 160 or more opioid pills (short acting or long acting), 90 or more long-acting pills, or any methadone pills or fentanyl patches in any calendar quarter.[11] We determined the prevalence of co-prescribed sedative-hypnotics overall and within each specific subgroup. Generalized estimating equations (GEE) logistic regression modeling, clustered on patients' primary clinic was used to identify factors associated with higher odds of being co-prescribed a sedative hypnotic. *P*-values less than .05 were considered statistically significant. This study was approved by the Oregon Health & Science University Institutional Review Board (STUDY00019177).

### Patient and Public Involvement

Patients were not directly involved in this research.

**Table 1.** Demographic and Comorbidities of Prescription Opioid Users who are Co-Prescribed Sedative Hypnotics, July 7, 2009 to 2018.

| | Patients with an opioid (%) | Patients co-prescribed sedative-hypnotic (%) | Percent of patients with an opioid and co-prescribed sedative-hypnotic |
|---|---|---|---|
| N | 240 587 (100%) | 55 332 (100%) | 23.0 |
| Chronic opioid use | 59 784 (24.9%) | 24 161 (43.7%) | 40.4 |
| Gender | | | |
| Male | 98 446 (40.9%) | 18 221 (32.9%) | 18.6 |
| Female | 141 984 (59.0%) | 37 070 (67.0%) | 26.1 |
| Other | 157 (0.1%) | 51 (0.1%) | 32.5 |
| Race/Ethnicity | | | |
| Non-hispanic white | 155 200 (64.5%) | 43 325 (78.3%) | 27.9 |
| Non-hispanic black | 30 131 (12.5%) | 4510 (8.2%) | 15.0 |
| Hispanic | 40 621 (16.9%) | 5062 (9.2%) | 12.5 |
| Other | 8393 (3.5%) | 1210 (2.2%) | 14.4 |
| Unknown | 6242 (2.6%) | 1225 (2.2%) | 19.6 |
| Age | | | |
| 19-44 | 104 247 (43.3%) | 20 746 (37.5%) | 19.9 |
| 45-64 | 105 981 (44.1%) | 27 137 (49.0%) | 25.6 |
| >64 | 30 359 (12.6%) | 7449 (13.5%) | 24.5 |
| Insurance | | | |
| Medicare | 49 418 (20.5%) | 14 974 (27.1%) | 30.3 |
| Medicaid | 103 260 (42.9%) | 21 779 (39.4%) | 21.1 |
| Commercial | 32 488 (13.5%) | 6892 (12.5%) | 21.2 |
| Uninsured | 40 071 (16.7%) | 8309 (15.0%) | 20.7 |
| Other/Unknown | 15 350 (6.4%) | 3378 (6.1%) | 22.0 |
| Co-morbidities | | | |
| Anxiety | 76 169 (31.7%) | 32 452 (58.7%) | 42.6 |
| Depression | 92 786 (38.6%) | 30 999 (56.0%) | 33.4 |
| AUD | 17 844 (7.4%) | 5317 (9.6%) | 29.8 |
| OUD | 10 411 (4.3%) | 4275 (7.7%) | 41.6 |
| Other SUDs | 24 419 (10.2%) | 7677 (13.9%) | 31.4 |
| Sleep disorder | 2927 (1.2%) | 1201 (2.2%) | 41.0 |
| Seizure disorder | 4715 (2.0%) | 1674 (3.0%) | 35.5 |

Abbreviations: AUD, alcohol use disorder; OUD, opioid use disorder; SUD, substance use disorders.

## Results

Between 2009 and 2018, 240 587 adult OCHIN patients were prescribed one or more opioid prescriptions. As shown in Table 1, 59% of these patients were female, 65% Non-Hispanic White, and 44% ages 45 to 64 years. More than half of these individuals were either on Medicaid (43%) or uninsured (17%). Depression (39%) and anxiety diagnoses (32%) were common. One quarter (25%) of individuals were on chronic opioid therapy.

Among these individuals, 55 332 (23%) were co-prescribed at least one sedative-hypnotic medication during the study period. The prevalence of co-prescribed sedative-hypnotics was markedly higher among those with chronic opioid therapy (40%), anxiety (43%), opioid use disorder (42%), sleep disorders (41%), and seizure disorder (36%). The most commonly co-prescribed sedative-hypnotics were lorazepam (38%), zolpidem (30%), clonazepam (24%), diazepam (21%), and alprazolam (21%) (Supplemental Table 1).

Table 2 summarizes the GEE logistic regression model of factors associated with co-prescribed sedative-hypnotics. Although nearly all factors were independently associated with having been co-prescribed a sedative-hypnotic, chronic opioid therapy (adjusted odds ratio (AOR) 2.33; 95% CI 2.25-2.42), and the diagnoses of anxiety (AOR 3.72; 95% CI 3.53-3.93) and sleep disorders (AOR 1.53; 1.39-1.68) were the strongest predictors. Races/ethnicities other than non-Hispanic White were all significantly associated with lower odds of having a co-prescribed sedative-hypnotic. Every passing year was associated with 7% lower odds (AOR 0.93; 95% CI 0.92-0.94) of having a co-prescribed sedative-hypnotic.

As shown in Figure 1, the prevalence of co-prescribed sedative-hypnotics initially increased before starting to

**Table 2.** Odds Ratios of Factors Associated with Co-Prescribed Opioids and Sedative-Hypnotics.

| N = 240 587 | aOR | 95% CI | *P* |
|---|---|---|---|
| Chronic opioid therapy | 2.33 | 2.25-2.42 | <.001 |
| Age category | | | |
| 19-44 | Ref. | | |
| 45-64 | 1.26 | 1.22-1.31 | <.001 |
| >64 | 1.13 | 1.05-1.23 | .002 |
| Sex | | | |
| Male | Ref. | | |
| Female | 1.38 | 1.34-1.42 | <.001 |
| Other/unknown | 1.39 | 1.03-1.87 | .029 |
| Race/ethnicity | | | |
| NH white | Ref. | | |
| NH black | 0.60 | 0.56-0.64 | <.001 |
| Hispanic | 0.64 | 0.60-0.68 | <.001 |
| Other/unknown | 0.72 | 0.68-0.76 | <.001 |
| Insurance | | | |
| Commercial | Ref. | | |
| Medicaid | 0.92 | 0.87-0.96 | .001 |
| Medicare | 1.25 | 1.19-1.33 | <.001 |
| Uninsured | 0.78 | 0.70-0.85 | <.001 |
| Other/unknown | 0.86 | 0.78-0.94 | .001 |
| Co-morbidities | | | |
| Anxiety | 3.72 | 3.53-3.93 | <.001 |
| Depression | 1.38 | 1.34-1.42 | <.001 |
| OUD | 1.38 | 1.30-1.46 | <.001 |
| Alcohol | 1.13 | 1.08-1.19 | <.001 |
| Other SUDs | 1.08 | 1.04-1.12 | <.001 |
| Sleep | 1.53 | 1.39-1.68 | <.001 |
| Seizure | 1.44 | 1.33-1.55 | <.001 |
| Year (cont.) | 0.93 | 0.92-0.94 | <.001 |

Abbreviations: aOR, adjusted odds ratio; NH, non-Hispanic, OUD, opioid use disorder; SUD, substance use disorder. Generalized estimating equation logistic model clustered by patients' primary clinic.

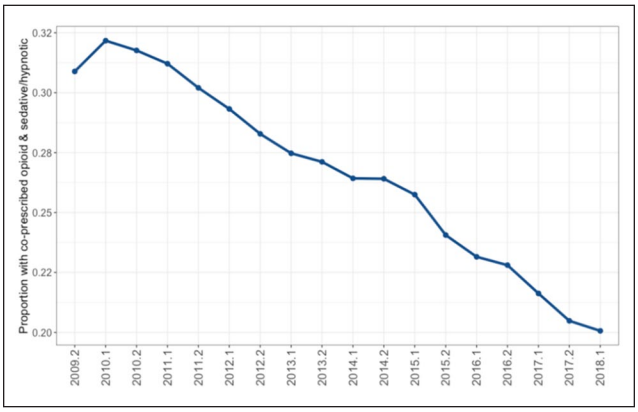


**Figure 1.** Proportion of patients with an opioid and co-prescribed sedative hypnotic.

decline in 2010. From its peak, co-prescribing declined from 32% in 2010 to 20% in 2018 (38% relative reduction). Declining trends in co-prescribed sedative hypnotics were similar across all demographic subgroups evaluated (Figure 2).

## Discussion

It is well established that the risk of opioid overdose is substantially increased with the co-administration of benzodiazepines and other sedative-hypnotics. Despite these risks, we found that more than 1 in 5 patients prescribed an opioid in a community health center were also prescribed a sedative-hypnotic prescription in the same 6-month period. The likelihood of a co-prescribed sedative-hypnotic was particularly high among individuals with chronic opioid therapy, those over 44 years in age, non-Hispanic Whites, females, those with Medicare insurance, and among individuals with mental health conditions (eg, anxiety, depression, OUD). Although the likelihood of being prescribed both medications has declined substantially between 2010 and 2018, the proportion with a co-prescribed sedative-hypnotic remained over 20% for those on chronic opioid therapy, Non-Hispanic Whites, females, and with individuals with Medicare or commercial insurance.

Overall, our findings differ markedly from other longitudinal studies of opioid-related polypharmacy. In a study of nearly 5 million patients with commercial or Medicare Advantage insurance who had recently filled an opioid prescription, Jeffery et al[10] observed only modest changes in proportion of patients with co-prescribed opioids and benzodiazepines between 2014 and 2018. Following the release of the CDC's chronic opioid prescribing guidelines, the largest declines were observed among those who were long-term opioid users. However, even among these patients, the proportion of patients with a co-prescribed benzodiazepine remained above 20% for both commercially insured and Medicare Advantage beneficiaries. Bohnert et al[8] found similar changes in benzodiazepine opioid co-prescribing among a nationally representative sample of individuals prescribed an opioid between 2012 and 2017. Another study that examined trends in co-prescribing following the FDA's boxed warnings in 2016 found significant, though modest, reductions in concurrent use.[9]

Although the rapid decline in co-prescribed sedative hypnotics is not consistent with trends in other populations, it does align with prior research on opioid prescribing in OCHIN community health centers. From 2009 to 2018, overall opioid prescribing in the OCHIN network declined 74% compared to 37% nationally.[11] Chronic opioid use, another high-risk prescribing indicator, declined even more dramatically from 8.1% to 1.9% (77% relative reduction)

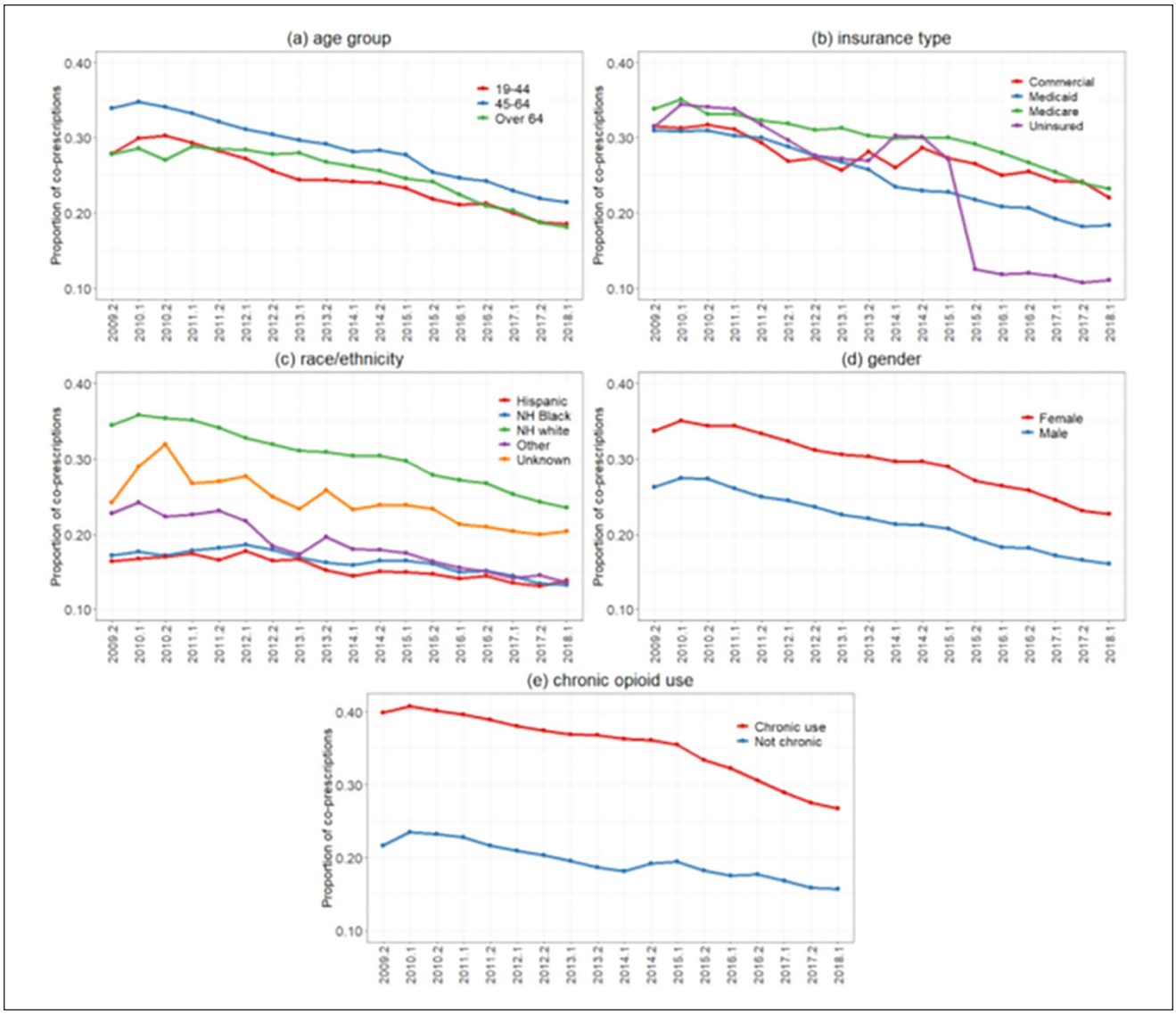


**Figure 2.** Proportion of patients with an opioid and co-prescribed sedative hypnotic by subgroup. (a) age group, (b) insurance type, (c) race/ethnicity, (d) gender, and (e) chronic opioid use.

during the same period. Other longitudinal studies of opioid prescribing have noted that larger declines are found in lower income populations. A nationally representative study using Medical Expenditure Panel Survey data, found that among patients reporting moderate or severe pain, opioid prescribing decreased by 2.6 percentage points between 2014 and 2016.[12] Although reductions were observed for all demographic groups, the largest decline was seen for those with incomes less than 100% of the federal poverty level (4.2 percentage points). Another study evaluated prescription opioid use in 4 different administrative pharmacy claims datasets (employer-sponsored commercial, Medicaid, Medicare, or a mix of commercial and Medicare Advantage) between 2002 and 2018 and found incident opioid prescriptions among those with Medicaid exhibited the largest declines (12.2% of those eligible in 2007-1.5% of those eligible in 2018).[13] Although the reasons for the more precipitous decline in co-prescribing are not completely clear, it could be due to extra caution taken by providers who are largely caring for socio-economically disadvantaged individuals disproportionately affected by the opioid epidemic.[14] This is consistent with the observation in this study that those with Medicaid or who were uninsured had the steepest decline and the lowest absolute rate of being co-prescribed a sedative-hypnotic. Another possible explanation is that CHCs, such as those included in the OCHIN network, were early adopters of innovative approaches at curtailing opioid related harms.[11,15,16]

The most notable change we observed was the steep decline in benzodiazepine co-prescribing among those who were uninsured which decreased from 27% to 13% in 2015. Closer inspection of those data reveal that this drop is likely explained by the large shift in patients' insurance coverage following the Affordable Care Act Medicaid expansion. Beginning in 2014, many OCHIN patients who were previously uninsured gained insurance, primarily through the Medicaid program. A previous study in the OCHIN network found that those who remained uninsured following the Affordable Care Act expansion were more likely to be Hispanic, which had among the lowest rates of benzodiazepine co-prescribing throughout most the study period.[17]

The lower rate of benzodiazepine co-prescribing in Hispanic and non-Hispanic Black individuals is also consistent with other research that suggests that racial disparities exist with respect to benzodiazepine use. Several epidemiologic studies have shown rates of benzodiazepine use are lower for non-Hispanic Black and Hispanic patients relative to White patients.[6,18-21] Rates of co-prescribing benzodiazepine with opioids have also been shown to be higher in White individuals relative to Black individuals.[10,22] It seems likely that disparities in benzodiazepine prescribing are related to the 3 to 4 fold higher rates of benzodiazepine-involved overdose experienced by White people relative to other racial groups.[23]

This study has limitations. First, data were derived from orders in the EHR and therefore may not reflect actual medications dispensed in pharmacies or what the patient actually consumed. Similarly, we had no information on when potential sedative-hypnotic refills were dispensed, and we considered orders issued within the same 6-month period to be co-prescribed. This may have erroneously misclassified some individuals as being co-prescribed a sedative-hypnotic, although the rates we observed are generally comparable to other investigations.[8,10] Finally, the OCHIN network grew rapidly during the study period and therefore our trends may reflect changing demographics and characteristics in the underlying study population. However, because our co-prescription outcome was operationalized as a proportion of patients who were prescribed an opioid, these changes seem unlikely to affect the trends reported.

In summary, we found that opioid-sedative-hypnotic co-prescribing declined substantially among CHC patients between 2010 and 2018. Although the frequency of co-prescribing declined in every demographic group, rates of co-prescribing remain elevated for several subgroups (chronic opioid therapy, females, Whites, Medicare, and commercially insured patients). Efforts to discourage new co-prescribing and facilitate deprescribing of sedative-hypnotics should continue to be developed and deployed in order to further reduce risks associated with opioid-related polypharmacy.

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## Author Contribution Statement

Concept and design: Muench, Hartung, Lucas Acquisition, analysis, or interpretation of data: Lucas, Huguet, Bailey, O'Malley, Voss, Chamine, Muench, Hartung

Drafting of the manuscript: Hartung, Lucas Critical revision of the manuscript for important intellectual content: Lucas, Huguet, Bailey, O'Malley, Voss, Chamine, Muench, Hartung

Statistical analysis: Lucas, Voss Administrative, technical, or material support: Voss, Chamine.

Supervision: Muench, Hartung

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Hartung is a research project consultant for Alkermes. No other authors have conflicts of interest to declare.

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## Supplemental Material

Supplemental material for this article is available online.

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