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SCIENTIFIC INVESTIGATIONS

Past-year use or misuse of an opioid is associated with use of a sedative-hypnotic medication: a US National Survey on Drug Use and Health (NSDUH) study

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Study Objectives: Prescription use and misuse of opioids are linked to greater sleep disturbance. However, there are limited data on the prevalence of sedative-hypnotic medication use among persons who use opioids. Therefore, this study examined whether past-year sedative-hypnotic use among persons who used/misused opioids was higher than among individuals who did not use opioids.

Methods: Data were acquired from the US National Survey on Drug Use and Health for 2015–2018. Use of a sedative benzodiazepine (temazepam, flurazepam, triazolam) or a Z-drug (eszopiclone, zaleplon, zolpidem) was examined in relation to use/misuse of an opioid within the past year. Logistic regression models estimated the associations between opioids and sedative-hypnotics using inverse probability of treatment weighting. A secondary machine learning analysis tested 6 binary classifiers to predict sedative-hypnotic use based on opioid use/misuse and other covariates.

Results: Of 171,766 respondents, 24% used a prescription opioid whereas 3.6% misused an opioid in the past year. Among those who used a prescription opioid, 1.9% received a sedative benzodiazepine and 9% received a Z-drug during the same time frame. Use of an opioid was associated with greater odds of sedative benzodiazepine use (odds ratio, 4.4; 95% confidence interval, 3.61–5.4) and Z-drug use (odds ratio, 3.8; 95% confidence interval, 3.51–4.09), and stronger associations were noted for misuse of an opioid. Machine learning models accurately classified sedative-hypnotic medication use for > 70% of respondents based on opioid use/misuse.

Conclusions: Sedative-hypnotic use is common among persons who use opioids, which is of concern given the elevated mortality risk with concurrent use of these substances.

Keywords: sleep initiation, maintenance disorders, opioid-related disorders, analgesics, opioids, hypnotics, sedatives, chronic pain

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Combined use of sedative-hypnotics and opioids increases the risk of overdose and death. However, there are minimal data on the prevalence of sedative-hypnotic use among individuals who use or misuse opioids.

Study Impact: In a nationally representative dataset, use of a prescription opioid increased the odds of using a sedative-hypnotic 4-fold in the past year, whereas misuse of an opioid was associated with a greater likelihood of sedative-hypnotic use. Use of an opioid and a sedative-hypnotic in the past year is common, and physicians should avoid prescribing both medications at the same time.

INTRODUCTION

Disrupted sleep is a common and undesirable corollary of long-term opioid use. More than 80% of persons who use opioids report poor sleep quality[1] or sleep continuity problems,[2] and 19%–37% report moderate to severe insomnia.[1,3–5] Higher opioid doses are also associated with less refreshing sleep and worse sleep maintenance.[2] In addition, objective measures tend to confirm self-reports of poor sleep,[1,6] although polysomnographic measures may normalize with chronic opioid use.[7] These sleep disturbances may result from multiple comorbidities in this population, such as depression, cigarette smoking, and pain.[8] Chronic pain is a significant cause of poor sleep,[9] and opioids are commonly prescribed for a wide range of acute and chronic pain conditions. However, opioid treatment only modestly improves self-reported sleep quality in persons with pain[10] (standardized mean difference of 0.36),[11] so mitigating pain may not be enough to resolve sleep disturbances. In addition, long-term opioid use for chronic pain is associated with disrupted sleep.[8,12] Individuals with opioid use disorder receiving maintenance medication treatment (eg, buprenorphine or methadone) report greater sleep disturbance than persons with opioid use disorder who are not on maintenance medication or who are receiving opioid antagonists.[4,5,13–15] Although opioids

are not known to cause sleep disturbance directly, acute opioid administration is known to reduce slow-wave sleep, which may increase feelings of daytime fatigue.[16] Alternatively, opioids increase the risk of central and obstructive sleep apnea,[7,8,10,11,17,18] which can manifest as unrefreshing sleep, frequent nighttime awakenings, and daytime somnolence. Regardless of cause, disrupted sleep is common among individuals using opioids and likely has a significant impact on patient quality of life and daytime functioning.

Sedative-hypnotic medications are a common treatment for sleep disturbances,[19–21] even among persons who use opioids. In a study of older adults who used opioids, 28% also received another central nervous system depressant, including 17.5% who received a nonbenzodiazepine sedative-hypnotic (so-called Z-drugs: zolpidem, eszopiclone, or zaleplon) and 32% who received a benzodiazepine.[22] In other words, approximately 5% of older adults who use opioids received a Z-drug and another 9% received a benzodiazepine during the same time frame, as compared to the 3% prevalence of prescription insomnia medication in the general population.[21] This overlap is of concern because opioids and sedative-hypnotics can both induce respiratory suppression, and users of opioids who receive a Z-drug are 3.67-fold more likely to die of an overdose even after adjusting for relevant confounders.[23]

Although these data indicate that the use of sedative-hypnotic medications is prevalent among persons who use opioids, large-scale population studies on this topic are scarce. Therefore, the present study used a nationally representative dataset to investigate the relationship between opioid use/misuse and the use of sedative-hypnotic medications. The primary hypothesis was that individuals who used or misused opioids would be more likely to use a sedative-hypnotic medication. The primary analysis used logistic regression models to estimate the association between opioid use and sedative-hypnotic use. A separate analysis used machine learning classifiers to determine the extent to which opioid use/misuse along with other study covariates could be used to correctly classify sedative-hypnotic use in the study population.

METHODS

Data source

Data from 171,766 respondents were compiled from the US National Survey on Drug Use and Health (NSDUH)[24] for the years 2015–2018, the only years with data on Z-drug use. The NSDUH is an annual survey directed by the Substance Abuse and Mental Health Services Administration in all 50 states and the District of Columbia. Recruitment uses census data to divide each state into subregions of equal population size and selects random addresses from within these subregions. Up to 2 respondents from each address are selected to complete the survey using computer-assisted interviewing. Survey responses are weighted to be representative of the civilian, noninstitutionalized population of the United States ages 12 years and older, although responses from individuals under 18 are excluded. These data are available at https://www.datafiles.samhsa.gov.

Variables

Two study outcomes were examined: past-year use of a sedative benzodiazepine (temazepam, flurazepam, or triazolam) and/or a Z-drug (eszopiclone, zaleplon, or zolpidem). The study exposure was level of opioid use ("no opioid use," "opioid use," or "opioid misuse"), which was measured by asking respondents to review a series of prescription and illegal opioids and report whether they had used these substances during the past year. Opioid misuse was defined as the use of prescription opioids not prescribed to the individual, use of opioids for reasons other than what they were prescribed for, or the use of illicit opioids. A case of opioid misuse consisted of respondents who responded positively to any of the 3 questions in the NSDUH questionnaire battery: prescription opioid that "was not prescribed for you," use of any prescription opioid that "was not prescribed for you," use of a prescription opioid "only for the experience or feeling it caused," or use of an illegal opioid (eg, heroin). Unfortunately, no data were reported on the duration or dosage of any medications or substances used. Covariates included age, sex, race/ethnicity, income, education level, marital status, metropolitan status (urban, suburban, or rural), and severity of mental illness experienced in the last year (none, mild, moderate, or serious). Mental illness severity was based on logistic regression models developed by the Substance Abuse and Mental Health Services Administration in 2012[25] that use past-year Kessler-6 scores, World Health Organization Disability Assessment Schedule scores, suicidal ideation, major depressive episodes, and age as predictors.

Statistical analyses

In the primary analysis, binomial logistic regression models were used to provide clinically interpretable estimates of the associations between opioids and sedative-hypnotics. Two models were constructed: an unadjusted model with level of opioid use as the only predictor, and an adjusted model in which the data were balanced on the covariates using inverse probability of treatment weighting[26] and adjusted for the same covariates. Weights were calculated as the average treatment effect for everyone and stabilized to reduce the influence of extreme observations. Diagnostic measures showed that the mean differences between exposure groups post–inverse probability of treatment weighting were 1% or less (data not shown), thus confirming adequate balancing. Associations estimated by logistic regression are reported as odds ratios (ORs) and 95% confidence intervals (CIs).

As a secondary analysis, a machine learning approach tested whether opioid use/misuse could be used to correctly classify sedative-hypnotic medication use. Six binary classifier algorithms were tested: regularized logistic regression, gradient tree boosting, support vector machines, random forests, naïve Bayes, and decision trees. Classifiers were trained using opioid use/misuse, sex, age, race/ethnicity, income, education, marital status, metropolitan status, body mass index, and severity of mental illness as predictors of sedative benzodiazepine use and Z-drug use. The dataset was divided such that 75% of cases were used for training the classifiers and 25% were used for testing model effectiveness. This data split was stratified by outcome to ensure sufficient users of sedative benzodiazepines and Z-drugs in each

subset. The training data were further down-sampled to match the number of users with an equal number of nonusers.

Each classifier was trained using 10-fold cross-validation repeated 5 times with optimal hyperparameters selected using a racing algorithm[27] optimized primarily according to the Matthews correlation coefficient (MCC).[28,29] The MCC measures the correlation between all observed and predicted outcomes, which is useful when outcomes are imbalanced and there is no need to maximize predicting one outcome over another. In the present study, the MCC measured the correlation between predictions of hypnotic use/nonuse with self-reported hypnotic use/nonuse. This method was preferred because only a minority of the participants were users of hypnotics, and the predictions of hypnotic use were not significantly more important than predictions of nonhypnotic use. The MCC ranges from –1 (predicted outcomes are universally opposite of the observed outcome) to +1 (predicted outcomes perfectly match the observed outcome), and an MCC of 0 is equivalent to random guessing. Two additional metrics were also measured: balanced accuracy, which averages the sensitivity and specificity of the classifier, and the receiver operating characteristic (ROC) area under the curve. Once an optimal classifier was identified, it was retrained on the data without the opioid use/misuse variable to determine how opioid use/misuse affected classifier performance. The final trained classifiers were then applied to the test set to determine final model performance.

All analyses were conducted in R (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria). The full code is freely available at https://github.com/atubbs-sleep/NSDUH_OpioidHypnotics.

RESULTS

Participant characteristics

Sociodemographic characteristics of the participants are presented in **Table 1** as raw counts and population-estimated percentage prevalence by level of opioid use. In the past year, an estimated 3.6% of the population misused an opioid, whereas an estimated 24.0% used a prescription opioid and 72.4% did not use an opioid. Compared to nonusers, individuals who used opioids were more likely to be older, female, and White, whereas individuals who misused opioids were more frequently younger, male, and White; had a lower income; and were nonmarried. Opioid use of any kind was more prevalent among individuals with more severe mental illness.

Among those who did not use an opioid, 0.4% reported using a sedative benzodiazepine and 2.6% reported using a Z-drug. By comparison, a greater proportion of those who used an opioid reported hypnotic use (1.9% used a sedative benzodiazepine and 9% used a Z-drug), whereas those who misused an opioid reported the highest proportion of hypnotic use (3.2% used a sedative benzodiazepine and 13.7% used a Z-drug).

Associations between opioid use and use of a sedative-hypnotic medication

In unadjusted analyses, individuals who used an opioid in the past year were significantly more likely to have used a sedative benzodiazepine (OR, 4.4; 95% CI, 3.61–5.40) or a Z-drug (OR, 3.8; 95% CI, 3.51–4.09) in the same period when compared with individuals who did not use an opioid. Balancing and adjusting for covariates did not substantially change these estimates. Similarly, in unadjusted analyses, a person who misused an opioid in the past year was more likely to have also used a sedative benzodiazepine (OR, 7.5; 95% CI, 5.98–9.34) or a Z-drug (OR, 6.1; 95% CI, 5.44–6.75) during the same period, and these estimates remained significant after adjusting for relevant covariates. These data are presented in **Table 2**.

Machine learning classification of sedative-hypnotic use among users of opioids

Using the MCC to select the optimal binary classifier, we found that regularized logistic regression showed the best performance in classifying users of Z-drugs (MCC = 0.175). Although support vector machines had the best MCC for classifying sedative benzodiazepine use (MCC = 0.092), the balanced accuracy and ROC area under the curve were significantly lower than the other classifiers (0.63 and 0.42, respectively), which indicated suboptimal performance. By contrast, regularized logistic regression had an only marginally lower MCC (0.089) while preserving balanced accuracy and the ROC area under the curve (0.73 and 0.80, respectively). Therefore, regularized logistic regression was chosen as the optimal classifier for sedative benzodiazepine use. The training performance of all 6 classifiers is presented in **Table 3** and **Figure 1**.

Having selected regularized logistic regression as the optimal classifiers for sedative benzodiazepine use and Z-drug use, the classifiers were trained on the data with and without opioid use/misuse as a predictor, and then all 4 classifiers were applied to the test data to measure model performance using the ROC area under the curve. For sedative benzodiazepine use, the addition of opioid use/misuse increased performance from 0.71 to 0.78, and including opioid use/misuse improved performance from 0.72 to 0.79 for Z-drug use. The classifier ROC curves for each outcome are presented in **Figure 2**.

DISCUSSION

In this analysis of nationally representative data, individuals who used or misused an opioid in the past year had greater odds of also using a sedative-hypnotic, even after adjusting for sociodemographic and clinical covariates. In addition, machine learning models accurately classified sedative-hypnotic use in nearly 80% of cases when opioid use/misuse was included, which was an absolute improvement of 7% over the same models without opioid use/misuse. Together, these findings emphasize the overlap between the use of a sedative-hypnotic and the use or misuse of an opioid.

Combined use of opioids and hypnotics increases the risk of overdose 2- to 3-fold,[23] and in this study an estimated 9% of those who used an opioid received a Z-drug and another 1.9% received a sedative benzodiazepine. Although it is impossible to tell whether the use of these medications overlapped (the NSDUH does not specify a period of use shorter than the prior year), the potential and risk for overlapping use are substantial. Indeed,

Table 1—Participant characteristics by level of opioid use.

	Past-Year Opioid Use			
	No Opioid Use	Opioid Use	Opioid Misuse	*P* Value
n	125,955	37,834	7,977	—
Age (y)				
18–25	43,202 (15)	9,058 (9.1)	3,430 (23)	< .001
26–34	25,643 (16)	7,684 (14)	2,088 (26)	
35–49	32,422 (25)	11,244 (25)	1,766 (26)	
50–64	13,998 (24)	5,769 (30)	566 (20)	
≥ 65	10,690 (20)	4,079 (23)	127 (4.7)	
Sex				
Male	60,591 (50)	15,000 (43)	4,246 (56)	< .001
Female	65,364 (50)	22,834 (57)	3,731 (44)	
Race/ethnicity				
White	73,116 (61)	25,189 (71)	5,393 (72)	< .001
Black	15,880 (12)	4,928 (12)	798 (10)	
Hispanic	23,555 (18)	4,736 (11)	1,062 (13)	
Native American	1,746 (0.5)	613 (0.6)	170 (0.8)	
Pacific Islander	641 (0.4)	186 (0.4)	39 (0.4)	
Asian	7,249 (6.8)	766 (2.5)	113 (1.6)	
Other	3,768 (1.5)	1,416 (2.1)	402 (2.5)	
Education				
College	35,782 (33)	8,880 (27)	1,317 (22)	< .001
Some college	40,169 (29)	14,305 (35)	3,073 (38)	
High school	33,090 (24)	10,157 (26)	2,373 (27)	
Less than high school	16,914 (13)	4,492 (12)	1,214 (14)	
Annual income ($)				
≥ 75,000	42,270 (39)	11,703 (35)	2,006 (30)	< .001
50,000–75,000	19,569 (16)	5,930 (16)	1,190 (16)	
20,000–50,000	39,066 (29)	12,247 (31)	2,655 (31)	
< 20,000	25,050 (16)	7,954 (18)	2,126 (23)	
Marital status				
Never married	58,102 (29)	13,708 (22)	4,876 (47)	< .001
Married	52,229 (53)	16,905 (53)	1,965 (33)	
Widowed	3,699 (5.7)	1,506 (6.8)	159 (3.2)	
Divorced/separated	11,925 (12)	5,715 (18)	977 (16)	
Metropolitan status				
Urban	58,769 (58)	15,344 (51)	3,351 (54)	< .001
Suburban	43,452 (29)	14,221 (33)	2,961 (31)	
Rural	23,734 (14)	8,269 (16)	1,665 (15)	
Mental illness severity				
None	103,722 (85)	26,737 (74)	4,151 (53)	< .001
Mild	11,394 (8.0)	4,876 (12)	1,306 (16)	
Moderate	5,788 (3.8)	3,031 (7.1)	1,059 (13)	
Serious	5,051 (2.9)	3,190 (7.0)	1,461 (17)	

Data are presented as n (population-estimated prevalence, %).

Table 2—The associations between opioid use and sedative hypnotic use in the NSDUH.

	Sedative Benzodiazepine Use		Z-Drug Use	
	OR	95% CI	OR	95% CI
Unadjusted				
Opioid use	4.4	3.61–5.40	3.8	3.51–4.09
Opioid misuse	7.5	5.98–9.34	6.1	5.44–6.75
Adjusted*				
Opioid use	3.6	3.28–3.99	3.4	3.18–3.57
Opioid misuse	7.2	5.62–9.22	6.4	5.63–7.27

*Adjusted/balanced for age, sex, race/ethnicity, income, education, marital status, metropolitan status, and severity of mental illness. CI = confidence interval, NSDUH = National Survey on Drug Use and Health, OR = odds ratio.

Musich and colleagues[22] noted that at least 60% of patients who were prescribed opioids and other central nervous system depressants received them both from the same provider, so it is critical that physicians and other prescribers consider alternative approaches before using sedative-hypnotic medications.[30] For example, a pilot crossover trial of 10 patients with opioid use disorder receiving methadone maintenance treatment found that mirtazapine alone improved insomnia indices compared to zolpidem or combination therapy.[31] Alternatively, meta-analytic data indicate that nonpharmacological sleep treatments, such as cognitive-behavioral therapy for insomnia, are effective in patients with chronic pain,[32] although a recent clinical trial found that cognitive behavioral therapy for insomnia failed to decrease either hypnotic or opioid medication use in patients with fibromyalgia.[33] Ultimately, more work is needed to identify effective and safe treatments for sleep disturbances in users of opioids.

The high proportion of sedative-hypnotic use among those who received an opioid tends to corroborate other reports of sleep disturbance among users of opioids. Although there is little evidence that opioids cause sleep disturbances, opioid use has been more prevalent among demographic groups at higher risk of sleep disturbance, which may increase the risk of concomitant use. For instance, individuals aged 50 years and older have been overrepresented among those using a prescription opioid, and older adults are more likely to report insomnia and other sleep disturbances.[34,35] Similarly, those with lower incomes are more likely to misuse opioids, and lower incomes are associated with sleep disturbances.[36–38] Thus, the high prevalence of poor sleep among users of opioids[4,14,15] may be a function of overlapping demographics in addition to an increased risk for sleep-related breathing disorders.[17,18,39] Unfortunately, the consequences of these disturbances are substantial; persistent poor sleep may exacerbate chronic pain[9] and impede progress toward remission in opioid use disorder, as has been shown in other substance use disorders.[8] Consequently, physicians who manage patients on long-term opioids should frequently screen for sleep disorders and refer at-risk patients to a sleep disorders clinic, which can order a sleep study to diagnose sleep-disordered breathing. Proper management of anxiety, depression, and other psychiatric disorders can also improve sleep disturbances and thus avoid resorting to sedative-hypnotic medications.

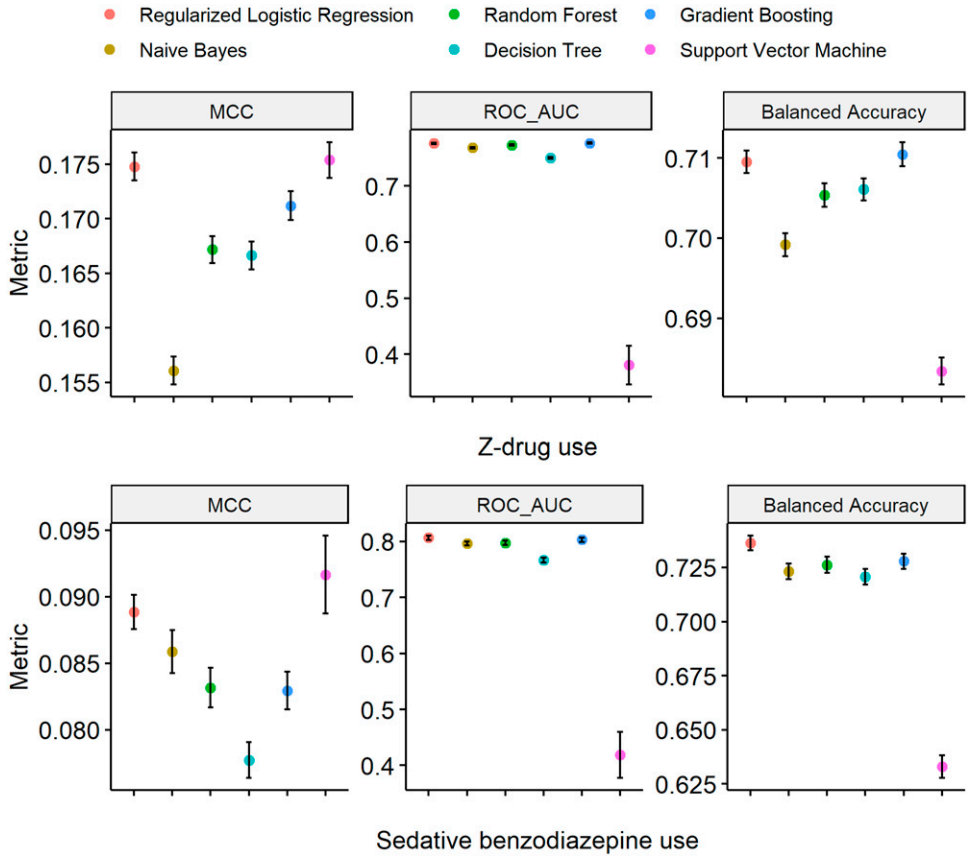
The machine learning analysis further supports the close association between opioids and sedative-hypnotics. Although predictions based on sociodemographic factors and severity of mental illness achieved slightly more than 70% accuracy, adding opioid use/misuse improved accuracy by an additional 7% for sedative benzodiazepines and Z-drugs. This finding provides secondary support to the primary conclusion that opioid use is closely associated with hypnotic use. Although opioids are not the sole determinant of an individual's hypnotic use, the use of an opioid should raise concerns for poor sleep or sleep-disordered breathing, particularly when combined with other clinical information.

Table 3—MCCs for each outcome across each classifier.

Classifier	Sedative Benzodiazepine Use	Z-Drug Use
Regularized logistic regression	0.089 (0.088–0.090)*	0.175 (0.174–0.176)*
Gradient boosting	0.083 (0.082–0.084)	0.171 (0.170–0.173)
Support vector machine	0.092 (0.089–0.095)	0.175 (0.174–0.177)
Random forest	0.083 (0.082–0.085)	0.167 (0.166–0.168)
Naive Bayes	0.086 (0.084–0.087)	0.156 (0.155–0.157)
Decision tree	0.078 (0.076–0.079)	0.167 (0.165–0.168)

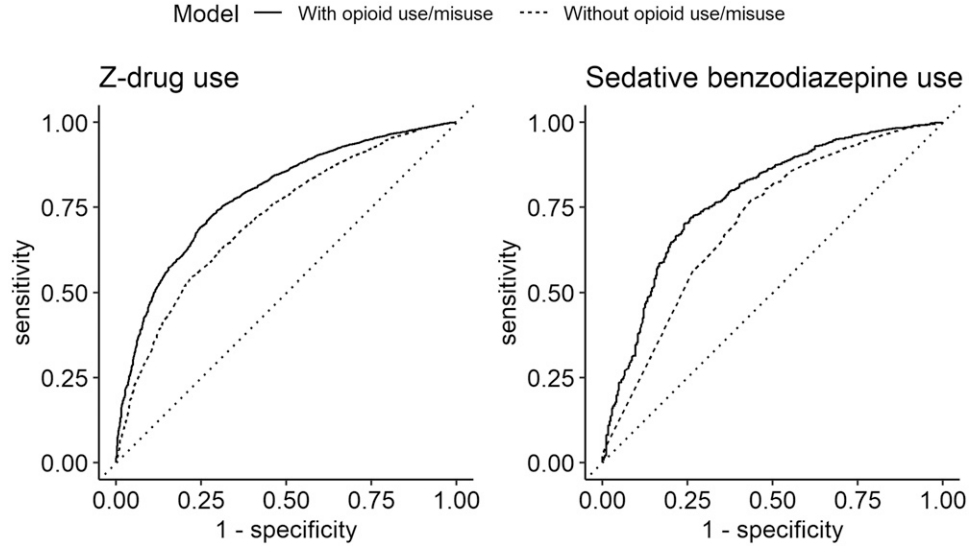
*Optimal classifier. MCCs reported as mean (95% CI). CI = confidence interval, MCC = Matthews correlation coefficient.

Figure 1—Comparison of classifier performance during the model training process.



Each of the 6 classifiers was used to classify Z-drug use (top row) and sedative benzodiazepine use (bottom row), with performance measured by 3 metrics: the MCC, the ROC AUC, and balanced accuracy. Higher values on each metric reflect better classification performance. MCC = Matthews correlation coefficient, ROC AUC = receiver operating characteristic area under the curve.

Figure 2—ROC curves using the final classifier model for each outcome.



The classification performance of the final models is represented as an ROC curve, in which increases in sensitivity are compared against decreases in specificity. The solid line represents the full model with opioid use/misuse included, and the dashed line represents the model with opioid use/misuse excluded. The diagonal line in the diagram shows the performance of a model built solely on random guessing. ROC = receiver operating characteristic.

The strengths of this study are the sample size (> 170,000 respondents) and the methodological rigor. Balancing and adjusting for numerous covariates as part of sequential logistic regression modeling reduced potential sample bias and increased confidence in the size and variance of the associations, and the machine learning analysis served as an effective secondary analysis to validate these results. In contrast, there are several limitations that should be considered when interpreting these data. First, self-report of the use/misuse of opioids and sedative-hypnotics during the past 12 months is an imprecise assessment prone to reporting and recall bias. Although such methods are common and practical in large, epidemiological surveys such as the NSDUH, more precise measures are needed to corroborate the present findings. Second, although participants reported the use of various medications and illicit substances, the quantity and duration of use were not reported, nor was the time frame beyond use within the last year. Thus, there is no way to confirm concurrent, sequential, or unrelated use of these medications and illicit substances during that window. A third limitation is the absence of questions or measures in the NSDUH that assess pain or sleep health,[40] which are critical components of mental health that likely impact substance use. Although analyzing sedative-hypnotic medication use provided a proxy for sleep disturbances, future iterations of the NSDUH should include validated measures of pain and sleep health to close this gap.

CONCLUSIONS

Opioid use has reached epidemic proportions in the United States, and disrupted sleep is often a companion of these substances. In analyzing data from a nationally representative sample, persons who used opioids were at least 4-fold more likely to use a hypnotic than persons who did not use opioids, and adjusting for sociodemographic and clinical covariates did not eliminate this relationship. Particular care should be taken when prescribing sedative-hypnotic medications to persons who use opioids, and nonpharmacologic evidence-based treatments for sleep disorders should be used in place of medications when possible.

ABBREVIATIONS

CI, confidence interval
MCC, Matthews correlation coefficient
NSDUH, National Survey on Drug Use and Health
OR, odds ratio
ROC, receiver operating characteristic

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