Concurrent Use of Opioids and Benzodiazepines: Evaluation of Prescription Drug Monitoring by a United States Laboratory

*Fred Leland McClure, PhD, MSci, F-ABFT, Justin K. Niles, MA,
Harvey W. Kaufman, MD, and Jeffrey Gudin, MD*

Objectives: Recently, more than 63% of the 52,404 drug overdose deaths in the United States involved heroin and opioid pain medications. More than 30% of opioid-related deaths also involved benzodiazepines. Previous studies examining the extent of concurrent opioid and benzodiazepine use have relied on prescription data. To gain fuller insight into the extent of the concurrent use problem, we analyzed opioid and benzodiazepine prescription patterns in the context of drug testing results.

Methods: All specimens from patients that were prescribed at least 1 drug and were tested for both opioids and benzodiazepines by a national reference laboratory were included. This resulted in an analytical set of 231,228 sets of test results from 144,535 patients with diverse demographic factors being tested in a variety of health care settings.

Results: Laboratory test results indicated concurrent use of opioids and benzodiazepines in over 25% of patients. In 52% of test results with evidence of concurrent use, 1 drug class was prescribed and the other was non-prescribed. Nearly 1 in 5 specimens (19%) testing positive for prescribed opioids also tested positive for non-prescribed benzodiazepines. Over 15% of specimens with prescribed benzodiazepines also demonstrated non-prescribed opioid use.

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Send correspondence to Fred Leland McClure, PhD, MSci, F-ABFT, Director, Medical Science Liaison, Medical Affairs—Quest Diagnostics, 11636 Administration Drive, St Louis, MO 63146.

E-mail: Leland.F.McClure@QuestDiagnostics.com.

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Conclusions: The extent of concurrent use of benzodiazepines and opioids, particularly non-prescribed use, suggests the need for more effective clinician assessment and intervention. The results support the Centers for Disease Control and Prevention opioid prescribing guidelines that drug testing occur before and periodically throughout opioid use and suggest that this testing should be extended to patients prescribed benzodiazepines as well.

Key Words: benzodiazepines, concurrent drug use, non-prescribed use, opioids, prescribed use

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Since 2000, the rate of opioid deaths in the United States has tripled (Rudd et al., 2016). Drug overdose deaths rose to the highest level ever recorded in 2015 and may have risen since. Over 63% of the 52,404 drug overdose deaths in 2015 involved heroin and opioid pain reliever medications (Rudd et al., 2016), and nearly half of these deaths involved prescription medications (Centers for Disease Control and Prevention (CDC), 2017). A number of risk factors have been identified that increase the risk of adverse events related to opioids, including concurrent use of benzodiazepine medications and other central nervous system depressants (Zedler et al., 2014). The cumulative and synergistic drug effects from combining benzodiazepines and opioids depress the central nervous system's medullary controls for respiration; benzodiazepines through the gamma-aminobutyric-acid receptors and opioids through mu (μ) and delta (δ) receptors. Some patients and individuals with substance use disorder may combine opioid and benzodiazepine drugs to increase the subjective peak strength of drug effects and sedation (Lintzeris et al., 2007), whereas others may use each drug therapeutically. In 2010, over 30% of opioid-related deaths in the United States also involved benzodiazepines (Jones et al., 2013). Of interest, among United States military veterans who were prescribed opioids and who subsequently died of a drug overdose, approximately half involved concurrent prescriptions for benzodiazepines (Park et al., 2015).

Federal agencies in the United States continue to make efforts to combat the opioid abuse and overdose epidemic. In August 2016 the United States Food and Drug Administration (FDA) issued a “boxed warning” on both prescription opioids and benzodiazepines alerting prescribers to the dangers of concurrent use (FDA, 2016). In March 2016, the CDC

released the CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. Two key recommendations are that clinicians “should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs” (Dowell et al., 2016). Drug testing prior to starting therapy with a controlled substance provides baseline information of current drug use. Subsequent drug tests monitor for both adherence with prescribed medications and abstinence from use of non-prescribed or illicit drugs. Drug testing patients who are prescribed opioids can reveal potentially dangerous drug combinations, including concurrent use of benzodiazepines, which can inform and affect clinicians’ treatment decisions.

Many studies have analyzed opioid (Pletcher et al., 2008; Jones, 2015) and benzodiazepine (Olfson et al., 2015; Jones, 2015) prescription data, and some have used this approach to appraise the extent of concurrent and potentially problematic prescribing (Paulozzi et al., 2015; Hwang et al., 2016; Stein et al., 2017). Considering that drug diversion and illicit use of both drug categories are known problems (The White House, 2012; Drug Enforcement Administration, 2013; Substance Abuse and Mental Health Services Administration, 2016), we believe it is important to understand not only prescribing patterns, but also how these patterns relate to actual patient drug use. Using a large national prescription drug monitoring database, we examined prescription data and urine drug testing data to determine the extent of concurrent use among patients undergoing drug testing for both opioids and benzodiazepines.

METHODS

Specimen Collections and Handling

The urine drug testing analyses included either presumptive immunoassay screens confirmed by quantitative definitive mass spectrometry, or only quantitative definitive mass spectrometry. The immunoassay presumptive screens for the benzodiazepines and opioids drug classes were performed using laboratory developed test procedures modified to detect compounds with low cross-reactivity (eg, 6-aminoclonazepam, lorazepam, hydromorphone). Quantitative confirmation analysis is performed to rule out false-positive presumptive screening results. The liquid chromatography-tandem mass spectrometry analysis was performed in clinical laboratories to provide sensitive and specific definitive quantitative analysis of the drugs and drug metabolites. All mass spectrometry methods were calibrated using reference materials traceable to the National Institute of Standards and Technology.

Study Data

All prescription drug monitoring test results with unique patient information within the Quest Diagnostics dataset that had at least 1 medication prescribed by the ordering physician from March 2015 through December 2015 and that were co-tested for both opioids and benzodiazepines were included. March 2015 was the first full month after we increased the number of drug analytes for this drug testing service from 26 to 44. A total of 131,012 patients were identified using a company-wide unique patient identification number and an

additional 13,523 were identified using a combination of date of birth, gender, ZIP Code, and insurance provider, combining for the 144,535 individuals in the analytical population. There were 231,228 test results from these individuals. All results were analyzed using the Quest Diagnostics medMATCH reporting service for tests of commonly prescribed and abused drugs. This service reports the presence of prescribed and non-prescribed drug(s) and drug metabolite(s) tested. Prescribed drug information is provided by the clinician ordering the test. Physicians ordering these tests are instructed to include information for all prescribed drugs for the patient, not just the drugs they have prescribed themselves. Many physicians use state prescription monitoring programs to check for other prescribed drugs before sending the information.

Drug Outcome Subgroups

For some drugs, the urine drug test may include multiple combinations of results in which parent drug(s) and drug metabolite(s) both represent drugs that may be prescribed. In these instances it was necessary to define the following analyte groupings that account for possible parent drug/drug metabolite relationships: codeine and morphine; hydrocodone and hydromorphone; oxycodone and oxymorphone; and nordiazepam, oxazepam, and temazepam. All groupings were counted positive if either the parent drug or metabolite(s) were present. Not all patients were tested for all subgroups: in some cases, individual subgroups were tested as a confirmation following a presumptive positive immunoassay result; in other instances, individual subgroups were tested in accordance with the laboratory test request. For example, a physician can order a test for oxycodone that, if presumptive positive, will reflex to a test for oxycodone, noroxycodone and oxymorphone or the health care provider may order a test for expanded opiates including oxycodone, noroxycodone, oxymorphone, codeine, hydrocodone, hydromorphone, morphine and norhydrocodone.

Demographic Factors

To account for potential changes during the study period, we analyzed demographic factors based on only the first examination for each patient. This study included test results of patients from 48 states in the United States. Data were analyzed in regions defined by the United States Department of Health and Human Services. Provider type information is linked to each Quest Diagnostics client account and/or individual provider. The demographics presented in Table 1 are intended to compare positive rates by characteristics within each group and the outcomes in each column are not mutually exclusive.

Statistical Analyses

Statistical significance testing of group proportions was conducted using the chi-square test. Trends in proportions of drug use among various groups were analyzed using the Cochran-Armitage test. The *t* test was used for significance testing of means. Multivariable logistic regression analysis was used to identify characteristics associated with prescribed and non-prescribed opioid and benzodiazepine use, as well as co-presence. To eliminate the possibility of correlated error due to some individuals having multiple test results we limited all logistic regression models to the each patient’s first test

TABLE 1. Opioid and Benzodiazepine Positives by Demographic Subgroups

	N	Positive for Opioid N (%)	Positive for Benzodiazepine N (%)	Positive for Both N (%)
Total	144,535	103,789 (71.8)	50,131 (34.7)	37,221 (25.8)
Male	60,436	44,171 (73.1)	17,581 (29.1)	13,406 (22.2)
Female*	83,433	59,082 (70.8)	32,269 (38.7)	23,573 (28.3)
Age < 18	878	61 (7.0)	39 (4.4)	22 (2.5)
18 ≤ Age < 25	3368	1632 (48.5)	697 (20.7)	448 (13.3)
25 ≤ Age < 35	15,816	10,319 (65.2)	4528 (28.6)	3164 (20.0)
35 ≤ Age < 45	23,986	16,609 (69.2)	7914 (33.0)	5751 (24.0)
45 ≤ Age < 55	36,587	26,806 (73.3)	13,075 (35.7)	9968 (27.2)
55 ≤ Age < 65	38,502	29,446 (76.5)	14,662 (38.1)	11,433 (29.7)
65 ≤ Age**	25,382	18,904 (74.5)	9210 (36.3)	6430 (25.3)
Primary care physician	61,484	42,401 (69.0)	21,969 (35.7)	16,017 (26.1)
Pain clinic	44,980	36,504 (81.2)	15,421 (34.3)	13,094 (29.1)
Drug rehab	2180	2002 (91.8)	341 (15.6)	304 (13.9)
Hospital	9288	4116 (44.3)	4132 (44.5)	1703 (18.3)
Neurology	3021	2454 (81.2)	997 (33.0)	838 (27.7)
Ob/Gyn	1130	738 (65.3)	368 (32.6)	262 (23.2)
Psychiatry	1522	766 (50.3)	573 (37.7)	283 (18.6)
Other/unspecified	20,930	14,808 (70.8)	6330 (30.2)	4720 (22.6)
Health and Human Services Region and States†				
1: CT, MA, ME, NH, RI, VT	5413	3546 (65.5)	1864 (34.4)	1283 (23.7)
2: NJ, NY	4076	3178 (78.0)	1137 (27.9)	900 (22.1)
3: DE, DC, MD, PA, VA, WV	9823	7359 (74.9)	3414 (34.8)	2676 (27.2)
4: AL, FL, GA, KY, MS, NC, SC, TN	56,923	39,840 (70.0)	21,459 (37.7)	15,155 (26.6)
5: IL, IN, MI, MN, OH, WI	25,673	18,796 (73.2)	8054 (31.4)	6135 (23.9)
6: AR, LA, NM, OK, TX	16,015	11,297 (70.5)	5999 (37.5)	4569 (28.5)
7: IA, KS, MO, NE	4432	3539 (79.9)	1604 (36.2)	1312 (29.6)
8: CO, MT, ND, SD, UT, WY	182	122 (67.0)	54 (29.7)	43 (23.6)
9: AZ, CA, HI, NV	20,458	14,991 (73.3)	6162 (30.1)	4859 (23.8)
10: AK, OR, ID, WA	1540	1121 (72.8)	384 (24.9)	290 (18.8)
Medicaid	12,780	8474 (66.3)	4229 (33.1)	3045 (23.8)
Medicare***	23,995	18,484 (77.0)	9309 (38.8)	7390 (30.8)
Private Payer	102,010	72,436 (71.0)	34,825 (34.1)	25,408 (24.9)

Note: 5750 missing payer type; 16 missing age; 666 missing gender.

†2-character standard state codes per the American National Standard Institute (ANSI).

*Statistically significant difference between males and females for all groups (chi-square $P < 0.01$).

**Statistically significant trend in age group proportions for all groups (trend $P < 0.01$).

***A significantly higher proportion of Medicare patients tested positive than patients with Medicaid or Private Payer status for all groups (chi-square $P < 0.01$).

result. We included variables that had a rate of concurrent benzodiazepine and opioid use higher than average for the study population in the unadjusted models. For area of residence, Health and Human Services Regions 3, 4, 6, or 7 were all included as separate binary variables. Being 35 years of age or older, having order codes originating from a pain clinic, primary care physician, and neurologist and having Medicare payer status were all included as binary variables. All variables from the unadjusted models were included in the testing of multivariable models because of their potential as confounding factors and to enable comparisons between models. Insignificant variables were removed from the multivariable models in backward stepwise fashion using a P value of < 0.05 . Test results with missing data for any of the variables were excluded from the adjusted models. All adjusted covariates are shown in the logistic model table. Results of adjusted and unadjusted models were stated as odds ratios (ORs) and 95% confidence intervals (95% CIs). Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). The proportional Venn diagram shown in Figure 1 was created using JMP version 11.0.0 (SAS Institute). This Quest Diagnostics Health Trends study was deemed exempt by the Western Institutional Review Board (Puyallup, Washington).

RESULTS

Demographic factors were captured at the time of each patient's first test result within the study period (Table 1). Of the 144,535 patients included, almost three-fourths tested positive for opioids and more than one-third tested positive for benzodiazepines. More than one-fourth of patients tested positive simultaneously for both opioid(s) and benzodiazepine(s).

The proportions of males and females testing positive for opioid medications were similar, but use of benzodiazepines and concurrent use of opioids and benzodiazepines was significantly more common among women than men ($P < 0.01$, Table 1). However, this was largely driven by women being prescribed benzodiazepines at a higher rate than men (32.7% vs 23.5%) as non-prescribed benzodiazepine use was similar between men and women (19.4% vs 15.2%). Use of opioids, benzodiazepines, and concurrent use of both drug classes demonstrated a significant increasing trend with age (all $P < 0.01$), but leveled off among those ≥ 65 years of age. Patients in pain clinics had the highest level of concurrent use. The frequency of concurrent drug class use varied with geographic region, being lowest in region 10 and highest in region 7. Medicare patients had significantly higher levels of opioid use, benzodiazepine use, and concurrent

FIGURE 1. Test results with concurrent use and types of concurrent use.

use than Medicaid patients and those with commercial insurance or private payer status (all $P < 0.01$).

Overall, 124,410 (86.1%) patients were prescribed at least 1 opioid, 41,599 (28.8%) patients were prescribed at least 1 benzodiazepine and 28,240 (19.5%) were prescribed both. 67.5% of specimens were positive for the opioid that was prescribed, 66.1% were positive for the benzodiazepine that was prescribed, and 58.9% were positive for both when both were prescribed. A breakdown of positivity for all study test results by prescribed and non-prescribed status is shown in Table 2. The majority of test results in the study were either negative for both benzodiazepines and opioids (15.9%) or positive for prescribed opioids only (43.1%). Of the 59,557 test results (25.8% of all results) that demonstrated concurrent use, 39,175 (65.8%) used at least 1 non-prescribed benzodiazepine or opioid. Other breakdowns of concurrent use are shown in Figure 1.

Nearly 1 in 5 results testing positive for prescribed opioids also tested positive for non-prescribed benzodiazepines (see Table, Supplemental Digital Content 1, <http://links.lww.com/JAM/A63>).

The hydrocodone subgroup was the most frequently prescribed opioid, and was most frequently found in combination with non-prescribed benzodiazepines. The nordiazepam/oxazepam/temazepam group was the most common non-prescribed benzodiazepine. The codeine, hydrocodone, and oxycodone subgroups followed similar concurrent use patterns; however, those testing positive for the methadone and buprenorphine subgroups showed different patterns of benzodiazepine subgroup positivity. There were 6292 test results with non-prescribed opioids in addition to prescribed benzodiazepines (15.5% of those positive for prescribed benzodiazepines—see Table, Supplemental Digital Content 2, <http://links.lww.com/JAM/A64>). The most commonly prescribed benzodiazepine was alprazolam. There were over 13,000 test results showing non-prescribed opioid use in the codeine subgroup and over 14,000 in the hydrocodone subgroups.

Of the test results positive for opioids, 21.6% were positive for multiple opioid subgroups. 13.6% of the test results that were positive for benzodiazepines were positive for multiple benzodiazepine subgroups. Of the test results

TABLE 2. Prescribed and Non-Prescribed Drug Classes (n = 231,228)

Positive for Prescribed Benzodiazepine (s)	Positive for Non-prescribed Benzodiazepine (s)	Positive for Prescribed Opioid (s)	Positive for Non-prescribed Opioid (s)	n (%)
No	No	No	No	36,687 (15.9)
No	No	No	Yes	7341 (3.2)
No	No	Yes	No	99,693 (43.1)
No	No	Yes	Yes	11,644 (5.0)
No	Yes	No	No	4823 (2.1)
No	Yes	No	Yes	2561 (1.1)
No	Yes	Yes	No	22,780 (9.9)
No	Yes	Yes	Yes	5015 (2.2)
Yes	No	No	No	10,544 (4.6)
Yes	No	No	Yes	2747 (1.2)
Yes	No	Yes	No	20,382 (8.8)
Yes	No	Yes	Yes	2378 (1.0)
Yes	Yes	No	No	939 (0.4)
Yes	Yes	No	Yes	567 (0.3)
Yes	Yes	Yes	No	2527 (1.1)
Yes	Yes	Yes	Yes	600 (0.3)

TABLE 3. Prescribed Use and Non-Prescribed Use Models

	Prescribed Opioid Use (n = 94,238)				Non-Prescribed Opioid Use (n = 20,768)			
	UOR	95% CI	AOR	95% CI	UOR	95% CI	AOR	95% CI
Female	0.91	0.89–0.93	0.90	0.88–0.92	0.94	0.92–0.97	0.96	0.93–0.99
Age ≥35	2.03	1.97–2.09	1.87	1.81–1.93	0.71	0.68–0.74	0.73	0.70–0.76
Pain clinic	1.92	1.87–1.97	2.32	2.24–2.39	1.12	1.08–1.15	1.17	1.13–1.22
Primary care physician	0.78	0.76–0.80	1.20	1.17–1.23	1.02	0.99–1.05	1.09	1.05–1.14
Neurology	1.79	1.65–1.95	2.55	2.33–2.79	0.89	0.80–0.99	NS	
Medicare	1.40	1.36–1.44	1.32	1.28–1.36	0.89	0.85–0.92	0.92	0.88–0.96
HHSR 3	1.00	0.96–1.04	0.89	0.85–0.93	1.61	1.53–1.70	1.43	1.35–1.51
HHSR 4	0.88	0.86–0.90	0.77	0.75–0.79	0.86	0.83–0.89	0.88	0.85–0.91
HHSR 6	0.98	0.95–1.01	0.89	0.85–0.92	0.85	0.81–0.89	0.85	0.80–0.89
HHSR 7	1.61	1.50–1.73	1.30	1.21–1.40	0.95	0.88–1.04	NS	

	Prescribed Benzodiazepine Use (n = 27,639)				Non-Prescribed Benzodiazepine Use (n = 25,610)			
	UOR	95% CI	AOR	95% CI	UOR	95% CI	AOR	95% CI
Female	1.50	1.46–1.54	1.51	1.46–1.55	1.34	1.31–1.38	1.35	1.31–1.39
Age ≥35	1.67	1.60–1.74	1.73	1.65–1.81	1.23	1.18–1.28	1.13	1.08–1.18
Pain clinic	0.52	0.50–0.54	0.44	0.43–0.46	1.67	1.62–1.72	1.88	1.81–1.96
Primary care physician	1.48	1.44–1.52	NS		0.80	0.78–0.82	1.15	1.11–1.19
Neurology	0.71	0.64–0.79	0.50	0.45–0.56	1.15	1.05–1.26	1.52	1.38–1.68
Medicare	1.20	1.16–1.24	1.10	1.06–1.14	1.16	1.12–1.20	1.18	1.13–1.22
HHSR 3	0.73	0.69–0.77	1.09	1.02–1.16	1.32	1.25–1.38	1.26	1.19–1.33
HHSR 4	1.47	1.43–1.51	1.76	1.71–1.82	0.94	0.91–0.97	0.90	0.88–0.93
HHSR 6	1.16	1.12–1.21	1.44	1.38–1.51	1.10	1.05–1.14	1.07	1.02–1.12
HHSR 7	1.06	0.98–1.14	1.50	1.38–1.62	1.05	0.97–1.13	NS	

	Prescribed Concurrent Use (n = 12,373)				Non-Prescribed Concurrent Use* (n = 24,848)			
	UOR	95% CI	AOR	95% CI	UOR	95% CI	AOR	95% CI
Female	1.33	1.28–1.38	1.33	1.28–1.39	1.32	1.28–1.36	1.33	1.29–1.37
Age ≥35	2.49	2.31–2.67	2.39	2.21–2.58	1.30	1.25–1.36	1.20	1.15–1.26
Pain clinic	0.76	0.73–0.80	0.86	0.81–0.91	1.59	1.54–1.63	1.80	1.73–1.87
Primary care physician	1.45	1.40–1.50	1.37	1.30–1.43	0.84	0.82–0.87	1.19	1.14–1.23
Neurology	1.05	0.93–1.19	NS		1.12	1.02–1.23	1.47	1.33–1.62
Medicare	1.47	1.41–1.54	1.29	1.23–1.35	1.20	1.15–1.24	1.20	1.16–1.25
HHSR 3	0.76	0.70–0.82	NS		1.27	1.20–1.33	1.26	1.19–1.33
HHSR 4	1.21	1.17–1.26	1.37	1.31–1.43	0.99	0.97–1.02	0.97	0.94–1.00
HHSR 6	1.29	1.22–1.36	1.42	1.33–1.50	1.07	1.02–1.12	1.07	1.02–1.12
HHSR 7	1.34	1.22–1.47	1.59	1.44–1.76	1.10	1.02–1.19	NS	

*Concurrent non-prescribed use includes all cases with concurrent use and at least 1 non-prescribed drug 6032 results (4.2%) were not included in the multivariable models due to missing variables.

AOR, adjusted odds ratio; CI, confidence interval; HHSR, Health and Human Services Region; NS, not significant and excluded from model; UOR, unadjusted odds ratio.

demonstrating concurrent use (see Fig. 1), 26.5% were positive for multiple opioid subgroups (including 6.7% of results positive for 3 or more subgroups), and 14.7% were positive for multiple benzodiazepine subgroups.

Multivariable models for prescribed and non-prescribed use of opioids and benzodiazepines, including concurrent use, are shown in Table 3. There are few consequential differences between the adjusted and unadjusted models; however, there are key differences between the prescribed and non-prescribed use models, most notably in patients age 35 or older and patients in pain clinics. Concurrent use models (both prescribed and non-prescribed) are noticeably more similar to benzodiazepine use models than opioid use models.

DISCUSSION

The findings of the present study suggest that analyzing the co-prescribing of opioids and benzodiazepines using available prescription databases and monitoring programs does not adequately assess the extent of this drug mixing

polypharmacy problem in the United States. The strength of this study is its scale, wide sex, age and geographic representation, and most critically, given the wide use of non-prescribed illicit drugs, its basis of actual laboratory measurement of drugs rather than relying on prescription data. More than 1 in 4 patients in this study had concurrent positive drug tests for both opioids and benzodiazepines. Nearly two-thirds (65.8%) of the test results that demonstrated concurrent use also showed non-prescribed use of at least 1 opioid or benzodiazepine. Over 4% of concurrent use results did not have prescriptions for either drug. This supports the previous assertions that benzodiazepine use among those undergoing chronic opioid therapy is non-prescribed and possibly recreational (Jones et al., 2012; Gudín et al., 2013).

Positivity for prescribed benzodiazepines and prescribed opioids was found in 11.2% of all test results. This is similar to the 9.6% reported in an analysis of millions of patients filling opioid and benzodiazepine prescriptions (Hwang et al., 2016). However, this sharply contrasts with

the 25.8% of all test results that were positive for any type of concurrent use. We also found that a large number of the 59,557 results demonstrating concurrent use tested positive for multiple drugs within the groups, particularly opioids. This likely magnifies the dangers of accidental drug overdose from misuse by these patients. It seems clear that concurrent prescribing is only a part of the concurrent use problem facing the United States. The amount of patients who did not test positive for their prescribed drugs is also concerning. Patients may not take their prescribed drugs due to undesirable side effects, or because they are no longer in pain; others may not be able to afford them; some patients may sell or give their drugs to others (diversion); in rare cases patients may be rapid metabolizers of the prescribed drug making the drug or metabolite undetectable at the time of testing.

With over 18% of test results positive for prescribed opioids demonstrating concurrent non-prescribed benzodiazepine use, the data presented in this study substantiate the recommendations by the CDC for drug testing of patients receiving opioid pain relievers. However, the data presented here also indicate that non-prescribed opioid use among those with benzodiazepine prescriptions is also a critical factor in the overall pattern of concurrent use. Over 15% of results testing positive for prescribed benzodiazepines also tested positive for non-prescribed opioids. This alarming frequency suggests that drug testing should be strongly considered by health care providers not only when prescribing opioid medications, as the CDC suggests, but when prescribing benzodiazepines as well.

As expected with high rates of opioid use relative to benzodiazepine use in the study population, concurrent use was largely driven by benzodiazepine positivity. This is evident in the multivariable models for both prescribed and non-prescribed drug classes. There are interesting differences between the prescribed and non-prescribed adjusted models. Those age 35 years or older and those with Medicare payer status were significantly more likely to test positive for prescribed opioids; however, both groups were significantly less likely to test positive for non-prescribed opioids.

Strengths of this study include that the data presented represent a large cohort (over 230,000 test results from over 140,000 patients) with great representation of sex, age, and geographic location. Our ability to analyze drug testing data allowed us to examine this polypharmacy problem at the utilization level and compare that to the prescription level. Subgroup drug testing data allowed for analyses to determine the extent of polypharmacy use within the greater opioid and benzodiazepine groups.

We also recognize some study limitations. Opioid and benzodiazepine subgroup analytes can be metabolites of multiple drugs, including prescribed drugs, which limited the amount of detail provided in the subgroup analyses. Physician prescribing information may not be complete for all patients in the study. We were not provided information about whether testing was witnessed or not. With nearly 72% of the patients in this population testing positive for opioids, it is possible that the index of suspicion for drug misuse is higher in this population. Thus, this population is more likely to be representative of a prescription drug-monitored cohort than the general population in the United States. Given the new

opioid prescribing guidelines released by the CDC recommending drug testing for all patients who are prescribed opioid medications, it is also possible that some selection bias in the population may be reflecting the physicians already using best practices in drug prescribing.

CONCLUSIONS

The data presented in this study demonstrate that the extent of concurrent use of benzodiazepines and opioids goes well beyond what is indicated by analyzing prescription data alone. The data also support CDC recommendation that drug testing occurs before and periodically throughout opioid use and suggests that this testing should be extended to benzodiazepine prescribing as well. Expansion of electronic Prescription Drug Monitoring programs in many states has greatly improved clinicians' ability to identify all prescription information for their patients in real time. Unfortunately, these programs cannot capture non-prescribed drug use. Clinicians should be aware of potentially dangerous drug interactions beyond the prescription level, and our data demonstrate these interactions are happening with alarming frequency. Insights gained through drug testing can inform health care providers, affect treatment strategies, and save lives.

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