Bamboo Health

PDMP Risk Factors and Unintentional Overdose Death

Kristine Whalen, PhD, David Speights, PhD,
Anjali Franco, MS, Renee Lindquist, MS, Adi Raz, DBA,
Jim Huizenga, MD, Data Sciences, Bamboo Health

January 2019

Table of Contents

PDMP Risk Factors and Unintentional Overdose Death

ABSTRACT

Patient prescription history reported to state Prescription Drug Monitoring Programs (PDMPs) is an essential tool to independently assess a patient's history of opioid use and inform physician prescribing behavior. Three states provided patient-level data for all unintentional overdose deaths (2015 for one state and 2016 for two additional states), which were then linked to PDMP prescriptions in the prior two years (N=5,804 decedents, N=10,121,741 non-decedents). Associations between a history of substance use disorder, high MME, concurrent sedative/narcotic use, multiple prescriber use, multiple pharmacy use, increased opioid utilization and unintentional overdose death are reported. All risk factors are strongly associated with unintentional overdose death, but history of substance use disorder and multiple pharmacy episodes have the strongest associations in all three states.

INTRODUCTION

In 2016 there were more than 63,600 drug-related overdose deaths in the United States.[1] More than 60% of drug overdose deaths are attributable to opioids.[2] To help curb the opioid crisis, in 2016 the Centers for Disease Control and Prevention (CDC) released evidence-based guidelines for prescribing opioids to patients with chronic pain.[4]

There are four main risk factors identified in the 2016 CDC report as indicative of potential opioid-related harms:

- **CDC Factor #1:** a patient history of overdose
- **CDC Factor #2:** a history of substance use disorder (SUD)
- **CDC Factor #3:** prescribing high opioid dosages (≥50 MME/day)
- **CDC Factor #4:** concurrent benzodiazepine/ narcotic use.[4]

These risk factors can be assessed by (1) patient self-report, which may not be accurate or complete; (2) medical records, which may not include medications or diagnoses from providers outside of a prescriber's own health system; or (3) Prescription Drug Monitoring Programs (PDMPs).

As of 2018, all states but one had a state-wide PDMP collecting information within the state that providers and pharmacies could use to independently verify a patient's controlled substance prescription history.[5–7] While there are variations between states in what information is required to be entered into the PDMP and how long those records are kept, PDMP patient reports allow health care providers to view not only a patient's controlled-substance prescription history, but also assess some of the patient's risk factors for opioid-related harms. The act of reviewing a patient's PDMP history prior to prescribing or dispensing an opioid prescription allows for providers and pharmacists to potentially intervene when dangerous or otherwise at-risk prescribing history is found. Three of the four risk factors identified by the 2016 CDC prescribing guidelines can be assessed or approximated using PDMP data. We argue additional PDMP metrics, indicative of multiple prescriber episodes, multiple pharmacy episodes, and increased opioid use are also important to accurately estimating patient risk of opioid-related harms.

METHODS

PDMPs are state-wide data repositories of all outpatient dispensations of controlled substances identified by each state as potentially harmful or subject to abuse. Bamboo Health manages the PDMP data for 42 states and territories; provides a platform for interstate PDMP data sharing for 44 states; integrates PDMP information into providers' electronic medical record workflow in 30 states; and provides a substance use disorder prevention and management platform called NarxCare that enables care coordination and adverse event risk assessment in more than 30 states and several national pharmacy chains. In 2017, Bamboo Health's PDMP system captured over 313.5 million controlled-substance prescriptions across the United States, 43.4% of which were classified as narcotics. Data for each controlled substance prescription is submitted to the PDMP by the pharmacy when the prescription is dispensed to the patient.

Three states using Bamboo Health's PDMP system have partnered with Bamboo Health to provide unintentional overdose death records to assess how unintentional overdose death is associated with various risk factors in the PDMP. Each state adjudicated their own lists of deaths that were drug-related and each used slightly different criteria to determine cause of death8 and for defining unintentional overdose death. Death data for State 1 included all unintentional opioid-related overdose deaths occurring between 2011-2016 (N=3,579), State 2 provided unintentional overdose deaths occurring between 2013-2016 (N=8,137), and State 3 reported unintentional opioid-related overdose deaths occurring from 2013-2015 (N=5,261). Opioid-related deaths could include deaths related to either prescription or illicit opioids, such as heroin. Decedent records included the individual's name, date of birth, gender, and date of death.

Death records provided by the states were linked to individual PDMP prescription histories by one of two methods: first by a strict first name, last name, and date of birth match. After strict matching, additional matching allowed for first name variants found an additional 9, 9, and 8 decedents that matched to state PDMP records in State 1, State 2, and State 3, respectively. Those decedents who did not match to state PDMP records were not significantly different in age or gender than those that did match in any of the three states.

Due to different state criteria for determining if a death was unintentional, if a death was related to an overdose, and if an overdose was opioid-related, the prevalence of each risk factor and the corresponding associations with death were analyzed separately for each state. Deaths from the most recent year of state-provided unintentional overdose death data were the outcome for this study. Decedent records from 2016 were used for States 1 and 2, while 2015 decedent records were used for State 3.

Dispensations from the two years prior to the most recent available year of overdose death records for each state (2014 and 2015 for States 1 and 2; 2013 and 2014 for State 3) were assessed to derive risk factors. All decedents from January 1, 2016-December 31, 2016 (N=686 State 1; N=3,264 State 2) and all decedents from January 1, 2015-December 31, 2015 for State 3 (N=1,854) were included and non-decedents who had filled at least one prescription in each state's final year of available overdose death data were included in the analysis. The total number of patients included in this analysis was N=2,394,836 from State 1; N=4,026,822 from State 2; and N=3,525,887 from State 3.

Six risk factors, described below, were identified for this paper. Unadjusted odds ratios and 95% confidence intervals (CIs) were calculated to assess the strength of the association of each risk factor with unintentional overdose death.

1. Patient history of substance use disorder was identified using those National Drug Codes (NDC) specifically approved by the Food and Drug Administration (FDA) only for medication assisted therapy (MAT), which are limited to certain formulations of buprenorphine.[9] Any patient having ever filled a prescription for one of these buprenorphine formulations (Appendix A) over the three-year analysis period was considered to have had a history of substance use disorder. [CDC factor #2].

2. Concurrent benzodiazepine and narcotic use was assessed by identifying all patients in the PDMP who had filled both a sedative (including benzodiazepines, barbiturates, z drugs, and other sedative formulations) and a narcotic prescription in the same calendar month/year. [CDC factor #4].

3. Morphine Milligram Equivalence (MME) per day was calculated for all individual narcotic prescriptions by using the CDC published MME conversion factor.10 To calculate MME, the conversion factor for the prescription's NDC code was multiplied by the number of pills dispensed in the prescription, and then divided by the prescription's days-supply. If the recorded days-supply was zero, it was assumed that the quantity of pills dispensed was equivalent to the days-supply (9 dispensations, 0.000% State 1; 20,108 dispensations, 0.029% State 2; 724,521 dispensations, 1.166% State 3). MME per day was not calculated for any formulations of buprenorphine.[10] Two threshold cutoffs (≥50 MME/day and ≥90 MME/day), as defined in the 2016 CDC prescribing guidelines, were examined in this analysis.[4] [CDC factor #3].

4. Having filled prescriptions at five or more different pharmacies/ dispensers (“pharmacies”) identified by the unique pharmacy DEA number recorded in the PDMP for each dispensation. [Bamboo Health factor #1].

5. Having filled prescriptions written by five or more unique providers as identified by the unique provider DEA number recorded in the PDMP for each dispensation. [Bamboo Health factor #2].

6. A MME ratio representing the rate of change of narcotic usage was calculated by adding the MME/day of each prescription filled during the year prior to the outcome year and comparing that to the sum of the MME/day of all prescriptions filled two years prior to the index year. A ratio of 2 or higher, indicating that the total MME of all prescriptions filled had at least doubled was used as a cutoff indicative of large increases in narcotic use. [Bamboo Health factor #3].

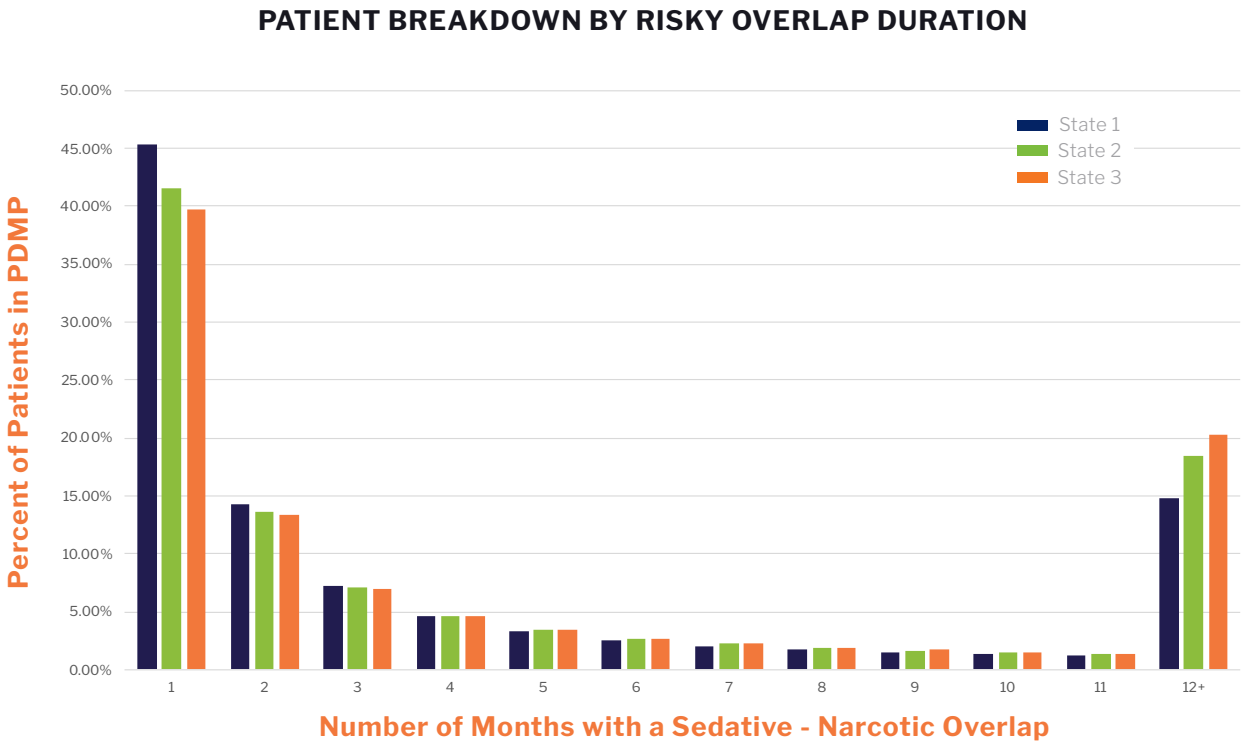


Figure 1: The percentage of patients with one or more months with both a sedative and narcotic prescription in the same month over a three-year period (N=488,539 State 1; N=778,149 State 2; N=835,066 State 3).

RESULTS

CDC RISK FACTORS AND DRUG-RELATED DEATH

Of the four CDC risk factors for adverse events in chronic opioid prescribing,[4] three can be identified or approximated using PDMP data. Patient history of substance use disorder (CDC risk factor #2), approximated by buprenorphine MAT use was present in 0.82% to 1.93% percent of patients in the PDMPs and associated with a 14.01 to 21.35 times increase in the odds of a drug-related death compared to PDMP patients without such a history. Concurrent sedative and opioid use (CDC risk factor #4) occurred in 18.50% to 23.68% of patients in the PDMPs during at least one month of the three years examined. The odds of a drug-related death for patients with an overlapping sedative and opioid prescription was 2.67 to 4.68 times higher than those PDMP patients who had never had a month with overlapping prescriptions (Table 1). Of the patients that had ever experienced a month with both a sedative and opioid prescription filled, between 14.75% and 20.23% of patients had an overlap in 12 or more months of their PDMP history (Figure 1).

CDC RISK FACTORS AND ASSOCIATION WITH DRUG-RELATED DEATH

Risk Factor	Area	Decedents			All Patients			Unadjusted or (95% CI)
		No. of Patients w/ Risk Factor	No. of Patients	% with Risk Factor	No. of Patients w/ Risk Factor	No. of Patients	% with Risk Factor	
Buprenorphine MAT History[1] [CDC factor #2]	State 1 State 2 State 3	103 758 264	686 3,264 1,854	15.01% 23.22% 14.24%	19,754 80,993 41,552	2,394,836 4,206,822 3,525,887	0.82% 1.93% 1.18%	21.35 (17.32, 26.34) 15.54 (14.33, 16.87) 14.01 (12.30, 15.96)
Concurrent Benzodiazepine - Opioid Use[2] [CDC factor #4]	State 1 State 2 State 3	374 1,231 1,094	686 3,264 1,854	54.52% 37.71% 59.01%	488,539 778,149 835,066	2,394,836 4,206,822 3,525,887	20.40% 18.50% 23.68%	4.68 (4.03, 5.44) 2.67 (2.49, 2.87) 4.64 (4.23, 5.09)
50MME or Higher[3] [CDC factor #3)	State 1 State 2 State 3	413 1,456 906	686 3,264 1,854	60.20% 44.61% 48.87%	721,471 1,247,550 972,033	2,394,836 4,206,822 3,525,887	30.13% 29.66% 27.57%	3.68 (3.08, 4.40) 1.58 (1.47, 1.70) 2.45 (2.22, 2.70)
90 MME or Higher[3] [CDC factor #3]	State 1 State 2 State 3	268 662 513	686 3,264 1,854	39.07% 20.28% 27.67%	276,382 401,363 330,079	2,394,836 4,206,822 3,525,887	11.54% 9.54% 9.36%	4.74 (4.03, 5.57) 2.06 (1.89, 2.25) 3.55 (3.20, 3.94)

Abbreviations: MAT: Medication Assisted Therapy; MME: Morphine Milligram Equivalence.
Table 1: CDC Risk Factors and Association with Drug-Related Death.

Note: PDMP records from all three states was limited to Jan. 1, 2014 through Dec. 31, 2016 (States 1 and 2) and Jan. 1, 2013 through Dec. 31, 2015 (State 3). Decedents were limited to deaths reported between Jan. 1, 2016 and Dec. 31, 2016 (States 1 and 2) and Jan. 1, 2015 and Dec. 31, 2015 (State 3). Non-decedents had at least one PDMP prescription fill between Jan. 1, 2016 and Dec. 31, 2016 (States 1 and 2) and Jan. 1, 2015 and Dec. 31, 2015 (State 3).

1. *Buprenorphine MAT history: defined as having a prescription for one of the GCN sequence numbers identified in appendix A.*
2. *Concurrent sedative – opioid use: defined as having had both a sedative and an opioid prescription filled in the same calendar month.*
3. *50/90MME: defined as ever having a prescription with an MME at or above the threshold.*

More than a quarter of PDMP patients in each state had ever had a prescription with a daily MME of 50 or more, and between 9.36% and 11.54% of the PDMP patients in each state had ever had a prescription with a daily MME of 90 or higher (CDC risk factor #3). The odds of a drug-related death when a patient had a history of a daily MME of 50 or more was 1.58 to 3.68 times higher, and if that history indicated ever having had a daily MME of 90 or more, was 2.06 to 4.74 times than those patients who did not meet those thresholds (Table 1).

PREVALENCE OF PROVIDER VISITS BY TYPE

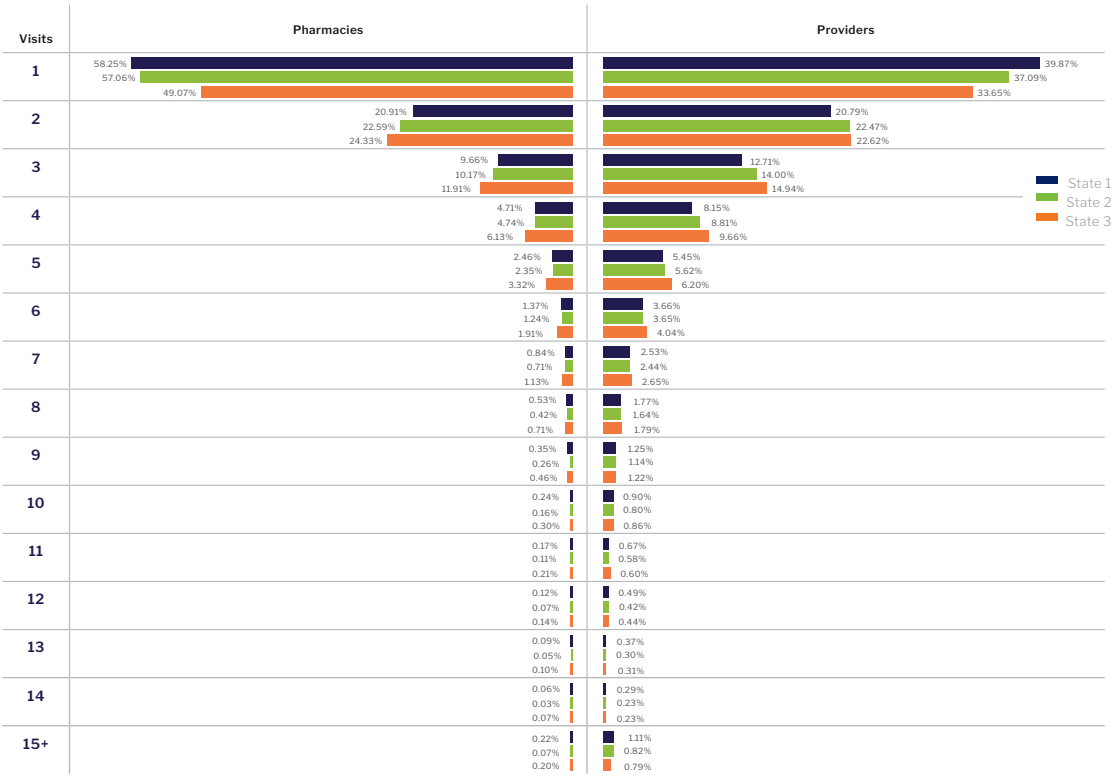


Figure 2: The distribution of number of pharmacies and number of providers per PDMP patient writing and filling controlled-substance prescriptions over three years (N=2,3,94,848 State 1; N=4,206,812 State 2; N=3,525,887 State 3).[1,2]

RESULTS

1. *Distinct pharmacies are identified by unique DEA numbers for the pharmacy filling the controlled substance prescription(s).*
2. *Distinct providers are identified by unique DEA numbers for the provider writing the controlled-substance prescription(s).*

ADDITIONAL RISK FACTORS AND DRUG-RELATED DEATH

In addition to the CDC identified risk factors, prior Bamboo Health research has emphasized the importance of identifying drug-seeking behavior in PDMP records. Three additional risk factors characterizing drug-seeking behavior were selected: filling prescriptions at five or more different pharmacies/dispensers ("pharmacies"), filling prescriptions written by five or more unique providers, and a MME ratio representing a rapid increase in narcotic usage, and drug-related death. Across the three states, between 6.46% and 8.55% of patients visited five or more pharmacies, and between 17.63% and 19.12% of patients had prescriptions written by five or more unique providers. Visiting 15 or more pharmacies was highly unusual (0.07%-0.22%), and between 0.79% and 1.11% of patients had 15 or more prescribers writing prescriptions over the three-year period (Figure 2).

ADDITIONAL RISK FACTORS AND ASSOCIATION WITH DRUG-RELATED DEATH

Risk Factor	Area	Decedents			All Patients			Unadjusted or (95% CI)
		No. of Patients w/ Risk Factor	No. of Patients	% with Risk Factor	No. of Patients w/ Risk Factor	No. of Patients	% with Risk Factor	
5 or More Pharmacies[1] [Bamboo Health factor #1]	State 1 State 2 State 3	222 851 627	686 3,264 1,854	32.36% 26.07% 33.82%	154,773 229,146 301,524	2,394,836 4,206,822 3,525,887	6.46% 5.45% 8.55%	6.93 (5.91, 8.14) 6.14 (5.68, 6.64) 5.47 (4.97, 6.03)
5 or More Providers[2] [Bamboo Health factor #2]	State 1 State 2 State 3	324 1,458 845	686 3,264 1,854	47.23% 44.67% 45.58%	442,528 741,713 674,197	2,394,836 4,206,822 3,525,887	18.48% 17.63% 19.12%	3.95 (3.40, 4.59) 3.78 (3.53, 4.05) 3.55 (3.24, 3.88)
MME Ratio ≥2[3] [Bamboo Health factor #3]	State 1 State 2 State 3	73 380 221	686 3,264 1,854	10.64% 11.64% 11.92%	147,919 256,996 214,787	2,394,836 4,206,822 3,525,887	6.18% 6.11% 6.09%	1.81 (1.42, 2.31) 2.03 (1.82, 2.26) 2.09 (1.81, 2.40)

Table 2: Additional Risk Factors and Association with Drug-Related Death.

Note: PDMP records from all three states was limited to Jan. 1, 2014 through Dec. 31, 2016 (States 1 and 2) and Jan. 1, 2013 through Dec. 31, 2015 (State 3). Decedents were limited to deaths reported between Jan. 1, 2016 and Dec. 31, 2016 (States 1 and 2) and Jan. 1, 2015 and Dec. 31, 2015 (State 3). Non-decedents had at least one PDMP prescription fill between Jan. 1, 2016 and Dec. 31, 2016 (States 1 and 2) and Jan. 1, 2015 and Dec. 31, 2015 (State 3).

Patients who filled prescriptions at five or more pharmacies were 5.47 to 6.93 times more likely to have died from a drug-related overdose. Patients who had prescriptions written by five or more providers were 3.55 to 3.95 times more likely to have died from a drug-related overdose (Table 2).

1. *5 or More Pharmacies: defined as filling prescriptions 5 or more distinct pharmacies/dispensers. Unique pharmacies identified using DEA numbers.*
2. *5 or More Providers: defined as having prescriptions written by 5 or more distinct providers. Unique providers were identified using DEA numbers.*
3. *MME Ratio ≥2: defined as the ratio of the total MME prescribed during 2015 (States 1/2) or 2014 (State 3) compared to the total MME prescribed in 2014 (States 1/2) or 2013 (State 3). Those with no history of narcotic prescriptions and therefore no MME in either pre-index year were considered to have no increase.*

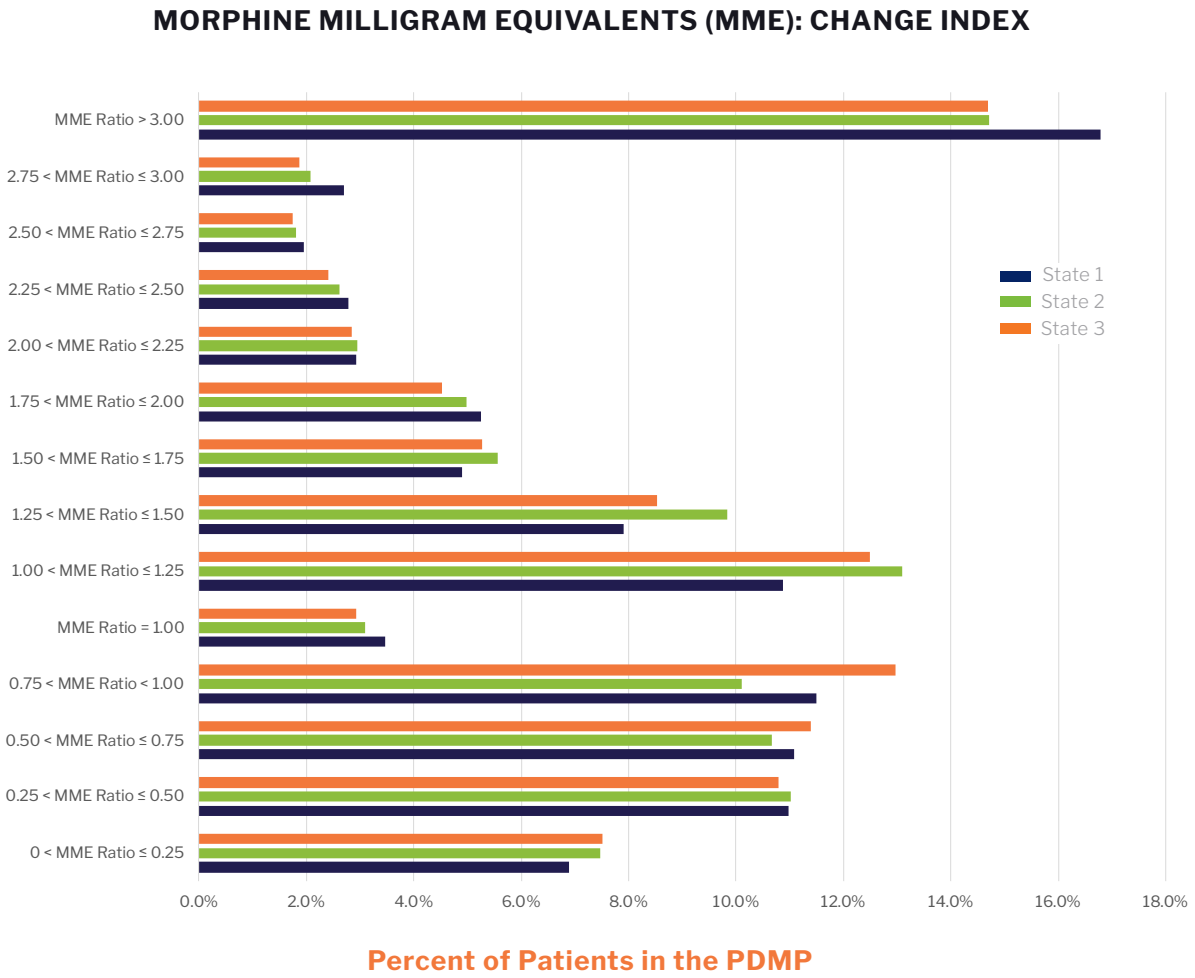


Figure 3: Distribution of MME Ratio among patients with opioid prescriptions in the two years preceding the most recent year of overdose death data from each state (N=509,259 State 1; N=1,008,385 State 2; N=875,226 State 3).[1]

1. *MME Ratio is the total MME prescribed in 2015 to 2015 (States 1 and 2) or 2014 to 2013 (State 3). Those patients without a narcotic prescription in either year were excluded.*

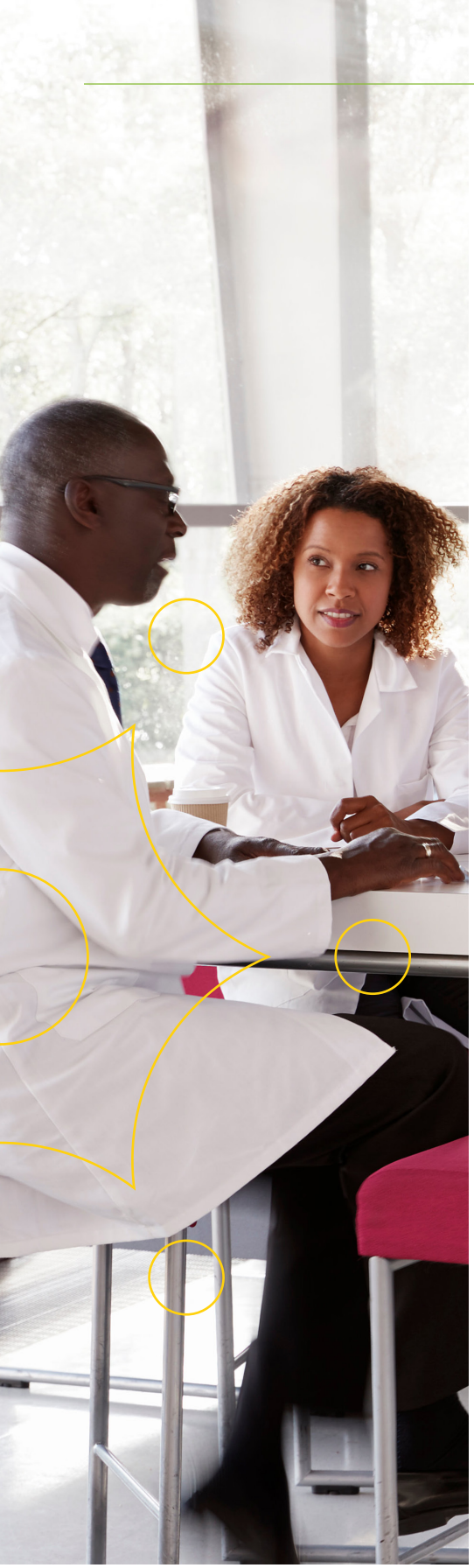
About 6% of all PDMP patients had at least doubled their total MME filled in the two years prior to the outcome assessment (Table 2), and 14.7% to 16.8% of patients who had narcotics scripts in both years more than tripled their MME (Figure 3). Patients whose MME ratio at least doubled were 1.81 to 2.09 times more likely to have died of a drug-related overdose than those who had not (Table 2).

CONCLUSIONS

The risk factors identified by the CDC for opioid-related harms and the other risk factors identified by Bamboo Health in the PDMP records are consistently and strongly associated with unintentional overdose death in three different states. PDMP records provide a unique opportunity to identify patients at risk of opioid-related harms using factors that are difficult to assess during patient interviews or through medical chart reviews. Using existing PDMP systems, multiple risk factors can be assessed and combined to provide a more accurate picture of which patients may need alternative medication options or alternative treatment methods. PDMP records and risk-scores are valuable tools to prescribers and pharmacists to assist in responsible narcotic prescribing.

Despite overdose death data that was identified differently in each of the three states, there were consistent and strong positive associations for each of the risk factors with drug-related death for all three states. History of substance use disorder was the strongest risk factor for unintentional overdose death despite being limited to only certain formulations of buprenorphine. It is important to note that treatment of substance use disorder with the medication assisted therapy buprenorphine is associated with improved outcomes compared to other treatment options.[11-33]

Identifying multiple prescriber episodes using the criteria of having filled prescriptions at five or more pharmacies or having had those prescriptions written by five or more providers is an important risk factor for physicians and pharmacists to assess when writing prescriptions or dispensing controlled-substance medications.



While filling prescriptions at five or more pharmacies was associated with a greater odds of unintentional overdose death than all but one other risk factor, having had prescriptions written by five or more prescribers was also strongly associated with unintentional overdose death and much more pervasive in the populations of each state. In this assessment of PDMP-identifiable risk factors and unintentional overdose death, the associations found were strong and consistent across three states.

The risk factors identified in this analysis are representative of the PDMP prescription history characteristics Bamboo Health is using to predict unintentional overdose death in their NarxCare product. The NarxCare overdose risk score uses a machine learning approach to assess the risk factors presented here and others. The patient's prescription history is examined over multiple time frames, assessing changes over time and highlighting recent changes in usage patterns to provide an estimate of overdose death risk. This approach allows for flexible prescribing, providing a risk assessment to the prescriber without limiting prescribing options.

In conclusion, there is significant value to utilizing PDMP records to identify new risk factors for overdose death. The risk factors identified through PDMP records are as strong or more strongly associated with unintentional overdose death than other established risk factors. Combining both commonly accepted risk factors with additional information identified from the state PDMPs can more accurately assess who is at risk of overdose death.

LIMITATIONS

There are limitations to this analysis. Death data were identified and verified by each state with different criteria and procedures for identifying an unintentional overdose death. Despite this, there were consistent and strong positive associations for each of the risk factors with drug-related death for all three states. State 2 was the only state that did not limit the decedents specifically to opioid-related unintentional overdose deaths, and as such, has slightly weaker associations with concurrent sedative–opioid use, with both daily MME thresholds, and with the number of pharmacies visited than the other two states. Yet the unadjusted odds ratios for all three states were remarkably consistent.

History of substance use disorder was the strongest risk factor for unintentional overdose death despite being limited to only certain formulations of buprenorphine. Other medication assisted therapies such as methadone and other treatment protocols for substance use disorder that do not include medication at all are not identifiable in the PDMP yet. Other research on the benefits and harms of treatments for SUD suggest that buprenorphine MAT is as safe, if not safer, than other forms of MAT or non-MAT treatment,[11–33] suggesting that the association of having a substance use disorder and subsequent overdose death observed in this analysis is likely to be an underestimate.

When calculating the prevalence of concurrent sedative and narcotic prescription use this analysis does not account for prescriptions that are filled at the end of one month that have sufficient supply for patients to still have access in subsequent months. On average, 75.5% of sedative prescriptions (77.1% State 1; 75.2% State 2; 74.7% State 3) and 38.8% of narcotic prescriptions (41.2% State 1; 34.6% State 2; 40.5% State 3) are written for 30 days or longer. This suggests the prevalence of overlapping prescriptions reported here could be an underestimate, and many more patients are at risk of drug interactions including death.[34–41] The MME per day threshold assessment in this analysis does not account for multiple active narcotic prescriptions, instead assessing each prescription alone. Therefore, the prevalence of a high daily MME is again likely to be an underestimate. Despite these limitations, this is the first assessment of PDMP-identifiable risk factors and associations with unintentional overdose death, and the associations found were strong and consistent across three states.

APPENDIX A.

GCN NUMBERS USED TO IDENTIFY BUPRENORPHINE MEDICATION ASSISTED THERAPY PRESCRIPTIONS.

GCN Sequence Number	Generic Name	Strength	Description
70259	BUPRENORPHINE HCL/ NALOXONE HCL	4 mg-1 mg	FILM, MEDICATED (EA)
70262	BUPRENORPHINE HCL/ NALOXONE HCL	12 mg-3 mg	FILM, MEDICATED (EA)
76145	BUPRENORPHINE HCL	74.2 mg	IMPLANT (EA)
29312	BUPRENORPHINE HCL	2 mg	TABLET, SUBLINGUAL
29313	BUPRENORPHINE HCL	8 mg	TABLET, SUBLINGUAL
51640	BUPRENORPHINE HCL/ NALOXONE HCL	2 mg-0.5 mg	TABLET, SUBLINGUAL
51641	BUPRENORPHINE HCL/ NALOXONE HCL	8 mg-2 mg	TABLET, SUBLINGUAL
66635	BUPRENORPHINE HCL/ NALOXONE HCL	2 mg-0.5 mg	FILM, MEDICATED (EA)
66636	BUPRENORPHINE HCL/ NALOXONE HCL	8 mg-2 mg	FILM, MEDICATED (EA)
71189	BUPRENORPHINE HCL/ NALOXONE HCL	1.4 mg-0.36 mg	TABLET, SUBLINGUAL
71190	BUPRENORPHINE HCL/ NALOXONE HCL	5.7 mg-1.4 mg	TABLET, SUBLINGUAL
72449	BUPRENORPHINE HCL/ NALOXONE HCL	2.1 mg-0.3 mg	FILM, MEDICATED (EA)
72450	BUPRENORPHINE HCL/ NALOXONE HCL	4.2 mg-0.7 mg	FILM, MEDICATED (EA)
72451	BUPRENORPHINE HCL/ NALOXONE HCL	6.3 mg-1 mg	FILM, MEDICATED (EA)
73424	BUPRENORPHINE HCL/ NALOXONE HCL	8.6 mg-2.1 mg	TABLET, SUBLINGUAL
73425	BUPRENORPHINE HCL/ NALOXONE HCL	11.4 mg-2.9 mg	TABLET, SUBLINGUAL
74685	BUPRENORPHINE HCL/ NALOXONE HCL	2.9 mg-0.71 mg	TABLET, SUBLINGUAL
76981	BUPRENORPHINE HCL/ NALOXONE HCL	0.7 mg-0.18 mg	TABLET, SUBLINGUAL

REFERENCES

1. *Hedegaard H, Warner M, Miniño AM. Drug Overdose Deaths in the United States, 1999-2016. NCHS Data Brief. 2017;(294):1-8. http://www.ncbi.nlm.nih.gov/pubmed/29319475. Accessed June 19, 2018.*
2. *Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445-1452. doi:10.15585/mmwr.mm655051e1*
3. *Dowell D, Arias E, Kochanek K, et al. Contribution of Opioid-Involved Poisoning to the Change in Life Expectancy in the United States, 2000-2015. JAMA. 2017;318(11):1065. doi:10.1001/jama.2017.9308*
4. *Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Reports. 2016;65(1):1-49. doi:10.15585/mmwr.rr6501e1*
5. *Paulozzi LJ, Kilbourne EM, Desai HA. Prescription Drug Monitoring Programs and Death Rates from Drug Overdose. Pain Med. 2011;12(5):747-754. doi:10.1111/j.1526-4637.2011.01062.x*
6. *Pardo B. Do more robust prescription drug monitoring programs reduce prescription opioid overdose? Addiction. 2017;112(10):1773-1783. doi:10.1111/add.13741*
7. *Paulozzi LJ, Strickler GK, Kreiner PW, Koris CM, Centers for Disease Control and Prevention (CDC). Controlled Substance Prescribing Patterns — Prescription Behavior Surveillance System, Eight States, 2013. MMWR Surveill Summ. 2015;64(No. SS-9):1-14. doi:10.15585/mmwr.ss6409a1*
8. *Caucci L, Warner M. Selected Characteristics of Deaths Requiring Autopsy by State. Centers for Disease Control and Prevention. https://www.cdc.gov/phlp/docs/coroner/table2-autopsy.pdf. Published 2013. Accessed June 19, 2018.*
9. *Research C for DE and. Information by Drug Class - Information about Medication-Assisted Treatment (MAT). https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm600092.htm. Accessed June 28, 2018.*
10. *Analyzing Prescription Data and Morphine Milligram Equivalents (MME). https://www.cdc.gov/drugoverdose/resources/data.html. Accessed June 28, 2018.*
11. *Marsden J, Stillwell G, Jones H, et al. Does exposure to opioid substitution treatment in prison reduce the risk of death after release? A national prospective observational study in England. Addiction. 2017;112(8):1408-1418. doi:10.1111/add.13779*
12. *Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. Drug Alcohol Depend. 2009;105(1-2):9-15. doi:10.1016/j.drugalcdep.2009.05.021*
13. *Hickman M, Steer C, Tilling K, et al. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. Addiction. April 2018. doi:10.1111/add.14188*
14. *Soyka M. Treatment of opioid dependence with buprenorphine: current update. Dialogues Clin Neurosci. 2017;19(3):299-308. http://www.ncbi.nlm.nih.gov/pubmed/29302227. Accessed June 28, 2018.*
15. *Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction. 2003;98(4):441-452. http://www.ncbi.nlm.nih.gov/pubmed/12653814. Accessed June 28, 2018.*
16. *Bell JR, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. Drug Alcohol Depend. 2009;104(1-2):73-77. doi:10.1016/j.drugalcdep.2009.03.020*
17. *Giacomuzzi S, Kemmler G, Ertl M, Riemer Y. Opioid Addicts at Admission vs. Slow-Release Oral Morphine, Methadone, and Sublingual Buprenorphine Maintenance Treatment Participants. Subst Use Misuse. 2006;41(2):223-244. doi:10.1080/10826080500391845*
18. *Soyka M, Apelt SM, Lieb M, Wittchen H-U. One-year Mortality Rates of Patients Receiving Methadone and Buprenorphine Maintenance Therapy. J Clin Psychopharmacol. 2006;26(6):657-660. doi:10.1097/01.jcp.0000245561.99036.49*

19. *Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;(2):CD002207. doi:10.1002/14651858.CD002207.pub4*
20. *Hser Y-I, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. Addiction. 2016;111(4):695-705. doi:10.1111/add.13238*
21. *Hser Y-I, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109(1):79-87. doi:10.1111/add.12333*
22. *Bell J, Trinh L, Butler B, Randall D, Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. Addiction. 2009;104(7):1193-1200. doi:10.1111/j.1360-0443.2009.02627.x*
23. *Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. Drug Alcohol Rev. 2007;26(4):405-410. doi:10.1080/09595230701373834*
24. *Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017;2:CD002025. doi:10.1002/14651858.CD002025.pub5*
25. *Burns L, Gisev N, Larney S, et al. A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia. Addiction. 2015;110(4):646-655. doi:10.1111/add.12834*
26. *Kimber J, Larney S, Hickman M, Randall D, Degenhardt L. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. The Lancet Psychiatry. 2015;2(10):901-908. doi:10.1016/S2215-0366(15)00366-1*
27. *Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008;103(3):462-468. doi:10.1111/j.1360-0443.2007.02090.x*
28. *Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017;357:j1550. http://www.ncbi.nlm.nih.gov/pubmed/28446428. Accessed June 28, 2018.*
29. *Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ. 2010;341:c5475. http://www.ncbi.nlm.nih.gov/pubmed/20978062. Accessed June 28, 2018.*
30. *Maglione MA, Raaen L, Chen C, et al. Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: A systematic review. J Subst Abuse Treat. 2018;89:28-51. doi:10.1016/j.jsat.2018.03.001*
31. *Thomas CP, Fullerton CA, Kim M, et al. Medication-Assisted Treatment With Buprenorphine: Assessing the Evidence. Psychiatr Serv. 2014;65(2):158-170. doi:10.1176/appi.ps.201300256*
32. *Walker R, Logan T, Chipley QT, Miller J. Characteristics and experiences of buprenorphine-naloxone use among polysubstance users. Am J Drug Alcohol Abuse. April 2018:1-9. doi:10.1080/00952990.2018.1461876*
33. *Solli KK, Latif Z-H, Opheim A, et al. Effectiveness, safety and feasibility of extended-release naltrexone for opioid dependence: a 9-month follow-up to a 3-month randomized trial. Addiction. June 2018. doi:10.1111/add.14278*
34. *Kim HS, McCarthy DM, Mark Courtney D, Lank PM, Lambert BL. Benzodiazepine-opioid co-prescribing in a national probability sample of ED encounters. Am J Emerg Med. 2017;35(3):458-464. doi:10.1016/j.ajem.2016.11.054*
35. *Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ. 2015;350:h2698. http://www.ncbi.nlm.nih.gov/pubmed/26063215. Accessed June 29, 2018.*
36. *Kandel DB, Hu M-C, Griesler P, Wall M. Increases from 2002 to 2015 in prescription opioid overdose deaths in combination with other substances. Drug Alcohol Depend. 2017;178:501-511. doi:10.1016/j.drugalcdep.2017.05.047*
37. *Jones CM, McAninch JK. Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines. Am J Prev Med. 2015;49(4):493-501. doi:10.1016/j.amepre.2015.03.040*
38. *Stein BD, Mendelsohn J, Gordon AJ, et al. Opioid analgesic and benzodiazepine prescribing among Medicaid-enrollees with opioid use disorders: The influence of provider communities. J Addict Dis. 2017;36(1):14-22. doi:10.1080/10550887.2016.1211784*

39. *Schuman-Olivier Z, Hoeppner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ. Benzodiazepine use during buprenorphine treatment for opioid dependence: Clinical and safety outcomes. Drug Alcohol Depend. 2013;132(3):580-586. doi:10.1016/j.drugalcdep.2013.04.006*
40. *McClure FL, Niles JK, Kaufman HW, Gudin J. Concurrent Use of Opioids and Benzodiazepines. J Addict Med. 2017;11(6):420-426. doi:10.1097/ADM.0000000000000354*
41. *Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ. 2017;356:j760. http://www.ncbi.nlm.nih.gov/pubmed/28292769. Accessed June 29, 2018.*
42. *Leonhart MM, Rannazzisi JT, Caverly MW. Pharmacist's Manual. U.S. Department of Justice Drug Enforcement Administration Diversion Control Division. https://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html. Published 2010. Accessed July 2, 2018.*
43. *Rannazzisi JT, Caverly MW. Practitioner's Manual. U.S. Department of Justice Drug Enforcement Administration Diversion Control Division. https://www.deadiversion.usdoj.gov/pubs/manuals/pract/index.html. Published 2006. Accessed July 2, 2018.*

Bamboo Health

bamboohealth.com
9901 Linn Station Road | Louisville, KY 40223