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The Associations of Kratom (Mitragynine), Opioids, Other Substances, and Sociodemographic Variables to Drug Intoxication–related Mortality

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Introduction: The US age-adjusted drug overdose rate increased by 298%, with fentanyl being the main contributor to drug overdose deaths. The contribution of kratom to drug overdoses or intoxication is seldom reported despite its increasing use and detection among overdose decedents.

Methods: Our cross-sectional study utilized deidentified data from the Florida Department of Law Enforcement, 2020–2021 (N = 30,845). The medical examiners ascertained the exposures of interest (kratom, opioids, and other substances) and the outcome variable of drug intoxication–related mortality (DIRM) through autopsies and toxicology results. DIRM refers to any death from a substance identified as drug toxicity or intoxication. We used regression modeling to examine the association of exposure with DIRM.

Results: Five hundred fifty-one cases were confirmed kratom (mitragynine) exposures. More males died of DIRM (81.5%), primarily White (95.1%) and 35–44 years old (40.5%). Among mitragynine exposures, 484 (87.8%) died of DIRM; 36 decedents (6.5%) used kratom as the sole substance, and 515 (93%) used multiple substances; 437 (79.3%) used at least 1 opioid. The odds of dying of DIRM were 7.6 times higher among those mitragynine exposed compared with non–mitragynine exposed (univariate model) and 5.6 times higher after adjusting for confounders (multivariate model) (adjusted odds ratio = 5.6; 95% confidence interval, 4.1–7; $P < 0.001$). Opioid use increased the odds of dying of DIRM (adjusted odds ratio = 11.7; 95% confidence interval, 10.9–12.7; $P < 0.001$).

Conclusion: Our results indicate that dozens of decedents died of kratom (mitragynine) exposures alone, which has safety implications. Co-using opioids with kratom further increased the odds of dying of DIRM, indicating that kratom may not always work as a harm-reduction agent.

Key Words: decedents, drug intoxication, kratom, mitragynine, opioids

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Drug overdose or intoxication is a serious public health issue that has claimed the lives of more than 1 million Americans since 1999.[1] The US age-adjusted drug overdose deaths significantly increased by nearly 300%, from 8.2 deaths/100,000 standard population in 2002 to 32.6 deaths/100,000 in 2022.[2] Opioids, primarily fentanyl, were the main driver of drug overdose deaths.[3] However, the contribution of kratom in drug overdoses or intoxication is seldom reported despite its increasing use and detection among overdose decedents.

Intoxication results from repeated drug use or overingestion of a substance,[4] which is a significant cause of drug-attributable death. Drug use was also a risk factor for nearly 32 million disability-adjusted life-years (95% confidence interval [CI], 27.4–36.6) and 1.3% of all disability-adjusted life-years (0 = 95% CI, 1.2–1.5) in 2016 worldwide.[5] In the United States, drug overdoses have been steadily rising since 2016.[3]

The early documentation of kratom use in the United States coincided with a shift in opioid-prescribing practices and the landscape for substance use.[6] As opioid prescriptions became more tightly regulated, many individuals sought alternatives, including kratom.[6] Although some people turned to heroin when faced with reduced access to prescription opioids, others opted for kratom as a potential substitute or harm-reduction agent.[6] This substitution effect highlights kratom's appeal among those people seeking pain relief or withdrawal symptoms.[6] However, the full scope of kratom's use as a substitute for other substances or mitragynine's mechanism of action remains poorly understood.

Mitragynine is a natural indole alkaloid found in *Mitragyna speciosa*, known as kratom, a herbal tree of the

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coffee family native to Southeast Asia.[7] Hanapi et al[8] discussed the metabolic pathways of mitragynine and its potential drug interactions. Mitragynine binds at the opioid receptors in the body for its central analgesic effects, acting as a partial agonist with lower potency than morphine, and could be reversed by naloxone.[8] The presence of mitragynine in biological fluids served as a proxy for kratom use, which people consume as a tea, smoke its dried leaves, or ingest by capsules.[9] Recently, there has been an increased scientific and public interest in kratom. More than 2 million people in the United States used kratom in 2020, and more than 3 million in their lifetime.[10] A recent report suggests that there are about 10–15 million kratom users in the United States based on kratom-imported products from other countries.[11] People use kratom for self-treatment of pain and to improve endurance or as an alternative for opioid use and mitigation for substance withdrawal.[11-13] However, the US Drug Enforcement Administration listed kratom as a drug of concern,[14] with increasing reports of kratom-involved deaths,[15-17] which is an emerging public health concern. Kratom is banned in 15 countries and 6 states in the United States: Alabama, Arkansas, Florida, Indiana, Tennessee, and Wisconsin.[18]

Several factors may affect mitragynine's impact on health, particularly drug intoxication. Polysubstance use, for example, may result in unpredictable drug interactions and adverse effects, including death.[19] Age, sex, and comorbidities, such as heart and liver diseases, could have a pharmacotoxicological impact on a substance's absorption, distribution, metabolism, and elimination.[20] Although possible, there are very few people who ingest pure mitragynine. It is often part of a kratom preparation, which could be a native tea or concentrated extract.

Some people perceive kratom as safe and natural because it is plant-based.[21] However, there is limited information about kratom, including its adverse effects such as seizures, respiratory, and cardiac arrest, aside from the fact that this emerging substance can be addictive.[22] Kratom has a dose-dependent effect, which may explain its intoxicating outcome.[14] In low doses (about 1–5 g), kratom can have a stimulant effect, whereas higher doses (about 5–15 g) result in opioid-like symptoms.[23] The involvement of other substances with kratom drug intoxication, such as opioids, primarily fentanyl and morphine, remains unclear.

Our study population represents a subset of kratom exposures. We aim to (1) examine the associations of mitragynine with drug intoxication–related mortality (DIRM) within the available dataset, (2) determine the associations of opioids and other substances along with kratom in DIRM, and (3) examine the relationships between the sociodemographic variables of age, sex, race/ethnicity, and population density among those exposed to kratom with DIRM.

METHODS

Study Design

This cross-sectional study of decedents with any substances found in their system by the medical examiners uses deidentified data from the Florida Department of Law Enforcement (FDLE) from 2020 to 2021.[24,25] The study population included all age groups in all Florida counties (n = 67). The inclusion criteria included all decedents (or persons who died) with any substances detected in their system by the medical examiners as contained in the dataset (N = 30,845, 2 data years). No missing data were observed on the outcome of interest DIRM. No data were excluded in the analysis. However, we restricted our analysis to the covariates reported in the literature as having an association or relationship with drug intoxication. For example, we restricted our analysis to these substances that kratom users used (aside from opioids), such as benzodiazepines (coded yes or no, whether a decedent used any of these benzodiazepines such as alprazolam, temazepam, diazepam, nordiazepam, clonazepam, lorazepam, oxazepam, midazolam, and zolpidem; also, with stimulants such as amphetamine and methamphetamine; cannabinoids, ethanol, and cocaine).

Data Source

The investigator requested and obtained deidentified data from the FDLE from 2020 to 2021 for this study,[24,25] So far, these are the latest available data on the outcome of interest (kratom drug intoxication as indicated by the presence of mitragynine in biological samples) during this analysis. The FDLE datasets titled Drugs Identified in Deceased Persons are publicly available data, which included decedents across all age groups. The medical examiners coded the substances contained in the dataset as being present at the time of death or as a cause of death (COD) if the substance played a causal role in the death of a person, as determined through urine, autopsy, and toxicology results. For this study, we coded these substances (for primary and other exposures) as a binary (yes/no or present or not present at the time of death). Patient confidentiality is protected from these deidentified data. This study was approved by the Florida Atlantic University Institutional Review Board as an exempt nonhuman subject research.

Primary and Other Exposures

The primary exposure was kratom use (as indicated by the presence of mitragynine in biological sample analysis). Other exposures included are opioids (ie, fentanyl, fentanyl analogs, morphine, codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone, methadone, buprenorphine, tramadol, and heroin) and also benzodiazepines, stimulants, cocaine, cannabinoids, and ethanol in the same study years (2020–2021). The independent variables are the decedent's age, sex (male or female), race/ethnicity (White, Black, Hispanic, Asian, and other), population density (rural or urban counties), and clinical conditions, particularly diabetes and cardiac, liver, and kidney-related conditions (binary—present or not). The population density was coded using the 2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties, which classified counties into urban or rural counties through measures such as population size

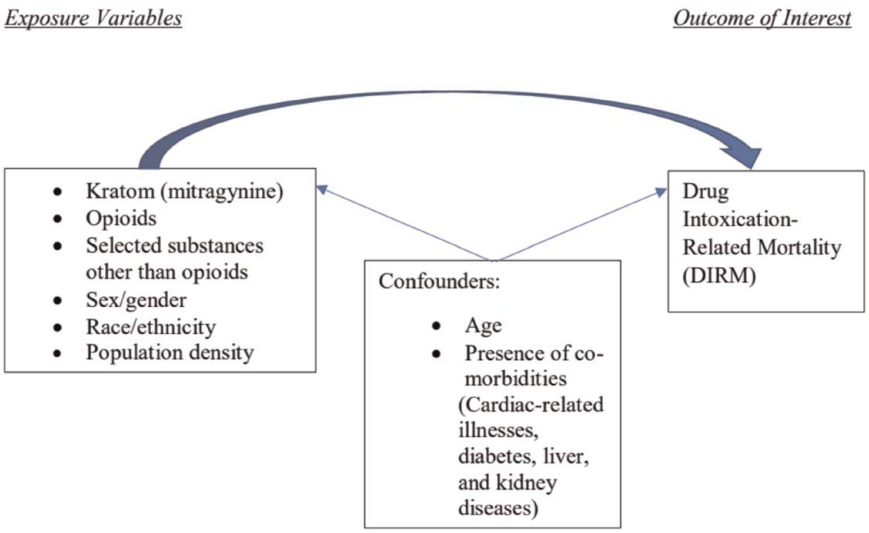

FIGURE 1. Directed acyclic graph (DAG) showing the relationship of exposure variables to drug intoxication–related mortality (DIRM).

of the Metropolitan Statistical Area as follows: urban or metropolitan large central metro (≥ 1 million people), large fringe metro (≥ 1 million but did not qualify as large central metro by National Center for Health Statistics), medium metro (250,000–999,999), and small metro ($< 250{,}000$), and for rural counties: micropolitan (10,000–49,999) and noncore ($< 10{,}000$).[26]

Primary Outcome of Interest

The primary outcome of interest is DIRM. For this study, DIRM is operationally defined as any death identified as drug intoxication or toxicity through autopsy and toxicology results by medical examiners. This outcome variable was dichotomized, whether the decedent died of intoxication or not (yes/no). The directed acyclic graph illustrates the relationship of these variables to the outcome of interest: DIRM (Fig. 1).

Statistical Analysis

Descriptive statistics describe the decedents' characteristics. We reported the mean and SD for the continuous age variable. In contrast, proportions for the binary and categorical variables of DI, sex/gender, race/ethnicity, population density, and drug use (either single drug or multiple drugs [polysubstance use]) are presented as frequencies and percentages. The Pearson χ^2 test of association examines the relationship between the exposure variables (age, sex/gender, race/ethnicity, population density, and comorbidity). Table 1 summarizes the characteristics of kratom users and nonkratom users among decedents found in the dataset.

Logistic Regression

We used univariable and multivariable logistic regressions to examine the associations between the exposures and the primary outcome DIRM as a binary variable (yes/no). The indicator method accounted for missing data, which was small ($n = 25$) for race/ethnicity. There are no missing data for the outcome of interest. The odds ratio (OR), 95% CI, and P values are also reported.

The selection of covariates for the model was guided by prior knowledge and aimed at controlling for variables that could influence the effect of drug exposure. This selection process was informed by clinical expertise, particularly concerning medical conditions known to affect drug distribution, absorption, metabolism, and excretion, which may contribute to intoxication risks. Specifically, we focused on conditions such as diabetes, liver disease, cardiac issues, and kidney problems, as these could elevate the likelihood of adverse drug reactions, including hepatotoxicity and nephrotoxicity, thereby increasing the potential for drug toxicity.[27,28,29]

These medical conditions—specifically diabetes, liver disease, cardiac issues, and kidney problems—are identified by medical examiners and are listed among the causes of death in the FDLE dataset. We reported the ORs, 95% CIs, and P values for our analyses, with the α level of significance set at 0.05. All data analyses were conducted using Stata 17 (StataCorp, College Station, Tex).

Confounders

The age (continuous) variable was used as a confounder. Older populations are often more at risk for drug intoxication, and age is usually associated with drug overdoses. Some clinical conditions are associated with drug-related mortality, that is, cardiac, diabetes, kidney, and liver-related conditions that may affect a drug's distribution, metabolism, and excretion.[27,28,29] We were interested in whether the presence of these conditions may influence DIRM and exposures of interest.

Effect Modification

We used interaction terms to account for the effect modification of kratom use and gender to drug in-

TABLE 1. Characteristics of Decedents with Mitragynine Exposures Versus Those Without Mitragynine Exposures in Florida, 2020–2021 (N = 30,845)

Characteristics	Mitragynine Exposures (n = 551)	Nonmitragynine Exposures (n = 30,294)	*P*
Age, mean (SD), y	38.1 (9.6)	45.6 (16.1)	
Age category, n (%)			< 0.001
0–17 y	0	404 (1.3%)	
18–24 y	31 (5.6%)	2163 (7.1%)	
25–34 y	179 (32.5%)	6044 (20%)	
35–44 y	223 (40.5%)	6500 (21.5%)	
45–54 y	77 (14%)	5764 (19%)	
55–64 y	38 (6.9%)	5782 (19.1%)	
≥ 65 y	3 (0.5%)	3637 (12%)	
Sex			< 0.001
Male	449 (81.5%)	22,257 (73.5%)	
Female	102 (18.5%)	8037 (26.5%)	
Race/ethnicity			< 0.001
White	524 (95.1%)	23,612 (77.9%)	
Black	11 (2%)	5112 (16.9%)	
Hispanic	14 (2.5%)	1185 (3.9%)	
Asian	1 (0.2%)	142 (0.5%)	
Other	1 (0.2%)	218 (0.7%)	
Missing	0	25 (0.1%)	
Population density, n (%)			0.03
Rural	13 (2.4%)	1058 (3.5%)	
Urban	538 (97.6%)	29,236 (96.5%)	
Opioids, n (%)			< 0.001
Opioid users	437 (79.3%)	15,816 (52.2%)	
Nonopioid users	114 (20.7%)	14,478 (47.8%)	
Drug use, n (%)			< 0.001
Single-drug users	36 (6.5%)	19,473 (64.3%)	
Multiple-drug users (2+)	515 (93.5%)	10,820 (35.7%)	
Drug intoxication, n (%)	484 (87.8%)	14,723 (48.6%)	< 0.001
Without drug intoxication	67 (12.2%)	15,571 (51.4%)	
Other substances			
Alcohol			< 0.001
Alcohol users	149 (27%)	12,379 (40.9%)	
Nonalcohol users	402 (73%)	17,915 (59.1%)	
Benzodiazepines			< 0.001
Benzodiazepine users	148 (26.9%)	6217 (20.5%)	
Nonbenzodiazepine users	403 (73.1%)	24,077 (79.5%)	
Cannabis/cannabinoids			< 0.001
Cannabis users	87 (15.8%)	7200 (23.8%)	
Noncannabis users	464 (84.2%)	23,094 (76.2%)	
Cocaine			< 0.001
Cocaine users	174 (31.6%)	7516 (24.8%)	
Noncocaine users	377 (68.4%)	22,778 (75.2%)	
Synthetic cannabinoids			0.5
Synthetic cannabinoid users	0	70 (0.2%)	
Nonsynthetic cannabinoid users	551 (100%)	30,224 (99.8%)	
Stimulants			0.3
Stimulant users	93 (16.9%)	5639 (18.6%)	
Nonstimulant users	458 (83.1%)	24,655 (81.4%)	
Clinical conditions			
With cardiac conditions	59 (10.7%)	5237 (17.3%)	< 0.001
No cardiac conditions	492 (89.3%)	25,057 (82.7%)	
With diabetes	3 (0.5%)	480 (1.6%)	0.051
Without diabetes	548 (99.5%)	29,814 (98.4%)	
With liver disease(s)	5 (0.9%)	482 (1.6%)	0.2
Without liver disease(s)	546 (99.1%)	29,812 (98.4%)	
With kidney problem	1 (0.2%)	159 (0.5%)	0.3
Without kidney problems	550(99.8%)	30,135 (99.5%)	

TABLE 2. Characteristics of Mitragynine-only Users (n = 36)

Characteristics	n	%	*P*
Age, mean (SD), 38.36 (10.02) y			
Age category			< 0.001
0–17 y	0		
18–24	2	5.56	
25–34	11	30.56	
35–44	14	38.89	
45–54	6	16.67	
55–64	3	8.33	
≥ 65	0		
Sex			0.78
Male	30	83.33	
Female	6	16.67	
Race/ethnicity			0.001
White	31	86.11	
Black/African American	2	5.56	
Hispanic	2	5.56	
Asian	1	2.78	
Other	0		
Population density			0.11
Large central metro	13	36.11	
Large fringe metro	10	27.78	
Medium metro	8	22.22	
Small metro	5	13.89	
Micropolitan	0		
Noncore	0		
Manner of death			< 0.001
Accidents	23	63.89	
Homicide	1	2.78	
Natural cause	5	13.89	
Suicide	7	19.44	
Undetermined cause	0		
Associated clinical conditions			
Cardiac-related	3	8.33	0.63
Diabetes	1	2.78	0.06
Kidney-related	0		
Liver disease	0		
Drug toxicity	20	55.60	< 0.001

The percentage for clinical conditions and drug toxicity does not sum up to 100% due to decedents having overlapping conditions, and not every decedent had one.

toxication, as well as kratom use and clinical condition to drug intoxication.

Sensitivity Analysis

For sensitivity analysis, a new variable, opioid count, was created to denote the number of opioids used by a decedent (1, 2, 3, 4, 5, and 6 or more opioids).

RESULTS

Decedent Characteristics

A total of 30,845 decedent cases from 2020 to 2021 were included in the analysis—15,207 decedents (49.3%) experienced drug toxicity; 551 cases tested positive for kratom (mitragynine). The mean age for mitragynine-positive cases was 38.1 (SD, 9.6). Mitragynine-positive cases were primarily male (81.5%) and White/Caucasians (95.1%); the 35- to 44-year age group (40.5%) was more affected, followed by the 25- to 34-year age group. In 353 of 551 cases of mitragynine-positive cases, the medical examiners determined mitragynine as a COD through toxicology results and autopsy. Among kratom users, 484 (87.8%) died of DIRM. The majority of them died in urban counties (97.1%); 59 kratom users had cardiac conditions. Among the clinical conditions, cardiac diseases were associated with drug intoxication among decedents who used kratom, which was statistically significant, $P \leq 0.001$. Table 1 summarizes the decedent's demographic characteristics.

Only 36 cases of mitragynine-positive cases used kratom as the sole substance, whereas the remaining (n = 515) co-used other substances. See Table 2 for the characteristics of these 36 mitragynine-only cases, including their COD. Among kratom users, 437 (79.3%) used at least 1 opioid. Fentanyl was the most detected opioid among mitragynine-positive cases (n = 398 or 72.2%), followed by fentanyl analogs (n = 218 or 24.1%). Table 3 summarizes the distribution of opioids among mitragynine-positive decedents.

The Associations of Kratom Use, Opioids, and Other Variables with Drug Intoxication

Table 4 summarizes the results of the univariable and multivariable logistic regression modeling with specified covariates. Using a univariate logistic regression, the odds of dying of drug intoxication among kratom users were 7.6 times higher compared with nonkratom users (OR = 7.6; 95% CI, 5.9–9.9; $P < 0.001$). On a multivariable logistic regression model, the odds of dying of DIRM among those who used kratom were 5.6 times higher compared with nonkratom users, after adjusting for confounders, which is statistically significant (OR = 5.6; 95% CI, 4.1–7.6; $P < 0.001$).

For the effect modification, there was no difference in the effect of kratom use by gender on drug intoxication, $P = 0.34$. There was also no difference in the effect of kratom use among those with cardiac conditions on drug intoxication, $P = 0.42$. However, kratom use and cardiac conditions by gender showed significant results. Thus, the other clinical conditions were removed from the model due to fewer cases or the number of decedents, which could bias the estimate.

For the sensitivity analysis, our results suggest that the more opioids a person took, the greater the odds of

TABLE 3. Distribution of Opioid (n = 12) Use Among Mitragynine Exposures versus Mitragynine Nonexposures in Florida, 2020–2021 (n = 903)

Opioids	Mitragynine Exposures, n (%)	Mitragynine Nonexposures, n (%)
Buprenorphine	9 (0.9)	504 (1.8)
Codeine	14 (1.6)	731 (2.6)
Fentanyl	398 (44.1)	11,824 (42.64)
Fentanyl analogs	218 (24.1)	4607 (16.61)
Heroin	45 (5)	1263 (4.6)
Hydrocodone	16 (1.8)	966 (3.5)
Hydromorphone	18 (2)	902 (3.3)
Methadone	11 (1.2)	748 (2.7)
Morphine	69 (7.6)	2764 (10)
Oxycodone	44 (4.9)	2254 (8.1)
Oxymorphone	24 (2.7)	1089 (4)
Tramadol	37 (4.1)	1045 (3.8)

TABLE 4. The Associations Between Exposure Variables and Drug Intoxication–related Mortality

	Univariate (Crude Analysis)			Multivariate (Adjusted Values)		
Covariates	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Decedents with mitragynine exposures (ref)	7.6	5.9–9.9	< 0.001	5.6	4.1–7.6	< 0.001
Nonmitragynine exposures						
Opioid users (ref)	16.9	16–19.7	< 0.001	11.7	10.9–12.7	< 0.001
Nonopioid users						
Age	0.98	0.98–0.98	< 0.001	0.98	0.98–0.99	< 0.001
Gender						
Male (ref)	1.3	1.2–1.3	< 0.001	1.2	1.1–1.2	< 0.001
Female						
Race/ethnicity						
White (ref)						
Black	0.44	0.41–0.47	< 0.001	0.58	0.53–0.63	< 0.001
Hispanic	0.75	0.67–0.85	< 0.001	0.78	0.66–0.91	0.002
Asian	0.5	0.35–0.70	< 0.001	0.62	0.39–1.0	0.05
Other	0.85	0.65–1.1	0.22	0.73	0.51–1.06	0.1
Population density						
Large central metro (ref)						
Large fringe metro	1.4	1.3–1.4	< 0.001	1.2	1.1–1.3	< 0.001
Medium metro	1.2	1.1–1.3	< 0.001	1.3	1.2–1.4	< 0.001
Small metro	0.9	0.84–1.02	0.17	0.88	0.77–1.01	0.06
Micropolitan (rural)	0.68	0.58–0.81	< 0.001	1.1	0.86–1.3	0.51
Noncore (rural)	0.45	0.37–0.55	< 0.001	0.5	0.38–0.64	< 0.001
Single- vs multiple-drug use (2+) (ref)	10.1	9.5–10.7	< 0.001	2.2	2.0–2.4	< 0.001
Other substances						
Alcohol use (ref)	0.45	0.43–0.47	< 0.001	0.96	0.9–1.03	0.3
Nonalcohol use						
Benzodiazepine use (ref)	1.6	1.5–1.7	< 0.001	0.84	0.78–0.91	< 0.001
Nonbenzodiazepine use						
Cannabis use (ref)	0.59	0.57–0.63	< 0.001	0.52	0.48–0.57	< 0.001
Noncannabis use						
Cocaine use (ref)	4.19	3.95–4.44	< 0.001	3.8	3.5–4.12	< 0.001
Noncocaine use						
Stimulant use (ref)	3.32	3.12–3.54	< 0.001	2.5	2.3–2.8	< 0.001
Nonstimulant use						
Synthetic cannabinoids (ref)	4.12	2.29–7.41	< 0.001	31.1	16.3–59.2	< 0.001
Nonsynthetic cannabinoids						
Clinical conditions						
Cardiac-related disease (ref)	0.37	0.35–0.39	< 0.001	0.49	0.46–0.54	< 0.001
Noncardiac						
Diabetes/diabetes-related conditions (ref)	0.26	0.21–0.32	< 0.001	0.48	0.37–0.63	< 0.001
No diabetes/diabetes-related conditions						
Kidney-related disease (ref)	0.3	0.20–0.43	< 0.001	0.44	0.28–0.70	< 0.001
No kidney-related disease						
Liver-related disease (ref)	0.43	0.35–0.52	< 0.001	0.71	0.55–0.91	0.008
No liver-related disease						

CI indicates confidence interval; OR, odds ratio.

dying of DIRM. For example, with 2 opioids, the odds of dying of DIRM were OR = 24.88 (95% CI, 22.86–27.09; $P < 0.001$); with 4 opioids, OR = 51.46 (95% CI, 40.32–65.66; $P < 0.001$); and for 6 opioids or more, OR = 87.46 (95% CI, 38.40–199.19; $P < 0.001$; Table 5).

TABLE 5. Sensitivity Analysis Examining the Association of Mitragynine with Drug Intoxication by Number of Opioid(s) Using Logistic Regression

Drug Intoxication	**OR**	**95% CI**	***P***
Mitragynine use	6.33	4.71–8.50	< 0.001
With 1 opioid	11.12	10.42–11.87	< 0.001
With 2 opioids	24.88	22.86–27.09	< 0.001
With 3 opioids	27.19	23.66–31.25	< 0.001
With 4 opioids	51.46	40.32–65.66	< 0.001
With 5 opioids	48.31	32.21–72.47	< 0.001
With ≥ 6 opioids	87.46	38.40–199.19	< 0.001

CI indicates confidence interval; OR, odds ratio.

DISCUSSION

This study examined the associations of kratom use, opioids, other substances, and sociodemographic variables with drug intoxication, which, to our knowledge, is the first statewide analysis of mitragynine-positive deaths. Our results indicated that more males died of drug intoxication than females (71.3%). Males (81.5%) used kratom more frequently than females (18.5%), and drug intoxications occurred more among Whites than non-Whites, which aligned with a previous study conducted by Grundmann[12] and Rogers et al,[30] showing similar sociodemographic profiles of kratom users. Our results indicated that the majority of the deaths related to kratom use mainly

occurred in urban counties. The use of kratom products is indicated by the presence of mitragynine in biological samples.[7,21] Rogers et al[30] reported that there was no definite profile of kratom users in the context of regionality or demographic setting, given the paucity of data on kratom. Nearly 54% of kratom users were from large metropolitan areas, which could explain the location of decedents with kratom use.[30]

Although most decedents used multiple substances, our results indicated that among those exposed to mitragynine, 36 (6.5%) of them had mitragynine as the sole substance found in their system at the time of death. In the absence of federal regulation and oversight, kratom should be viewed as a potential contributor or COD rather than a harmless herbal supplement.[31,32] Mitragynine was also detected as the sole causative agent in some fatality case reports.[33] Our results indicating polysubstance use among kratom users who died of drug intoxication also mirrored the results of a retrospective epidemiological study conducted by Olsen et al,[15] who reported 152 kratom-positive deaths with 7 reporting mitragynine as the only drug found in the analysis. Our results differ from those of Olsen and colleagues[15] by identifying 551 deaths over 2 data years from 2020 and 2021 limited to Florida, whereas Olsen and colleagues' study involved 27 states in the United States from July to December 2017. In addition, the 36 deaths from mitragynine exposure alone were higher than the 7 deaths that Olsen and colleagues reported from mitragynine exposure only,[15] which could indicate serious safety concerns from this substance.

Our results suggest that opioid use increases the odds of dying of DIRM among those exposed to kratom. This result is congruent with what Torrico et al[33] reported about the association of opioids with kratom death. However, Torrico and colleagues reported only 214 opioid-related deaths, in which 4 cases involved kratom in their study in 2020 in California.[34] In contrast, our previous study reported preliminary findings of more than 500 deaths associated with kratom use in 2020 and 2021 in Florida, which might suggest the underreporting of deaths from this substance.[35]

Strengths

One strength of this study is a larger sample size (N = 30,845). It is a state-wide analysis of decedents with any substance(s) found in their system at their demise, results of which could inform policymakers and local or regional stakeholders such as government agencies or institutions to tailor interventions from mitragynine-associated drug intoxication.

Limitations

This study is cross-sectional; therefore, no causal relationship between variables is inferred. The lack of granularity in the dataset, such as laboratory tests or vital signs before death, is missing, which is understandable given the nature of the subjects (decedents). The FDLE dataset did not specify if mitragynine was detected in blood plasma or tissues. Mitragynine is not part of the standard drug screening, at least in the United States.[36] More information is needed on whether the subjects came from a nursing home, independent living, hospice units, or acute care facilities and the severity of comorbidities. The statewide data could not be generalized to other states because the effects of kratom use could differ by state demographics. Similar studies in different regions could further enhance generalizability.

Because this is a secondary analysis, some information lacks granularity, such as no education, income, insurance status, drug dosage, the frequencies of drug(s) consumed or ingested by the users, or the route of drug consumption. There is no information on the disease severity of comorbidities in the dataset. In addition, there are no data to support whether the drugs included in the FDLE dataset were adulterated or not, which may increase the risk of drug intoxication. Access to granular data in prospective studies could provide a deeper understanding of the interactions between substances. Our sampling frame is DIRM, which may preclude accurate risk assessment. We recommend conducting a study with a broader cohort of kratom users and nonusers to assess the risks of death further. Conducting research that involved drug dosage and frequency and their associations with drug intoxication, particularly involving kratom, would be crucial to providing a comprehensive understanding of DIRM.

CONCLUSION

Drug intoxication is a serious public health issue that warrants more research, particularly on the mechanism of death from drugs' intoxicating effects. Our results have provided empirical evidence of the adverse outcomes where dozens of people died of drug intoxication from being exposed to mitragynine alone. Co-using other substances, particularly opioids, further increased the odds of dying of drug intoxication due to kratom exposure. Our results have safety implications as more people are using kratom, and young adults (25–44 years old) are mostly affected. Although there is no conclusive evidence on the impact of cardiac conditions on drug intoxication among kratom users, the public needs to be warned about this public health problem and heed the Food and Drug Administration's warning on kratom being a drug of concern.[37]

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