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RESEARCH REPORT

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Association between state-level kratom regulations and poison center-reported severe medical outcomes and healthcare use: A United States national analysis

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Abstract

Background and aims: Kratom use in the United States (US) has increased. Kratom is not federally scheduled; regulation is heterogenous and determined at the state level. Strategies include no regulation, bans and kratom consumer protection acts (KCPA) such as age limits, product purity or labeling requirements. Public health data informing these policies remain limited. This study aimed to compare rates of poison center (PC) reported kratom exposures, including those associated with severe medical outcomes and healthcare use, across US states with differing regulatory frameworks, and to characterize national trends in kratom exposures over time.

Design: Retrospective observational study of kratom exposures reported to the National Poison Data System from 2010 to 2023.

Setting: All 50 US states and the District of Columbia.

Participants: A total of 8919 kratom-related exposures were reported to PCs during the study period, including 5452 single-substance exposures (61%). Most cases involved adult males (69%), aged ≥18 years (8133; 91%).

Measurements: States were classified by kratom regulatory status into four categories: unrestricted (no regulations), KCPA, local restrictions (KCPA in 1 or more county, but no state regulation) or banned (retail sale illegal). The primary outcome was the incidence of severe medical outcomes defined as exposures coded by America's Poison Centers criteria as major effect (life-threatening or resulting in significant residual disability) or death. Secondary outcomes included rates of exposure, hospitalization and healthcare use (defined as hospital admission or evaluation in an emergency department, urgent care or primary care).

Findings: Kratom exposures increased from 19 cases in 2010 to 1242 cases in 2023 [incidence rate ratio (IRR) = 69.0 compared with 2010; 95% confidence interval (CI) = 39.6–120; $P < 0.001$]. Severe medical outcomes increased from zero cases in 2010 to 158 cases in 2023; 2012 was the first year in which a severe outcome was reported (2023 IRR = 56.9 vs 2012; 95% CI = 14.7–221; $P < 0.001$). Overall, 13% of kratom exposures resulted in a severe medical outcome. Compared with states where kratom was banned, statistically significantly higher rates of exposures (IRR = 2.49; 95% CI = 1.89–3.28), severe medical outcomes (IRR = 3.19; 95% CI = 1.78–5.70), healthcare use (IRR = 2.44; 95% CI = 1.66–3.60) and hospitalization (IRR = 2.45; 95% CI = 1.81–3.30,

$P < 0.001$) occurred (all $P < 0.001$). No statistically significant differences were identified between other regulatory categories.

Conclusion: Kratom exposures and severe medical outcomes reported to United States poison centers are increasing nationally, though states with bans in place have experienced less pronounced increases.

KEYWORDS
drug policy, harm reduction, Kratom, Mitragynine, opioids, poison center, substance use

INTRODUCTION

Kratom (*Mitragyna speciosa*), a Southeast Asian plant containing psychoactive alkaloids mitragynine and 7-hydroxymitragynine, has been used in traditional medicine for centuries, but has proliferated globally over the past two decades [1, 2]. Its psychoactive effects vary with dose, ranging from stimulant-like at low doses to opioid-like at higher doses [3, 4]. Common uses include managing chronic pain, depression, anxiety or opioid withdrawal, although robust evidence is lacking [5, 6].

Increased use has led to rising adverse health effects and healthcare utilization. From 2014 to 2024, 7333 emergency department or hospital visits related to kratom exposure were reported to United States (US) poison centers, with reported exposures increasing each year for the past decade [7]. Although poison center data are not population incidence data, this trend is concerning. More than half of these exposures reported adverse effects. Adverse effects from use can be mild, but also include severe symptoms such as cardiac dysrhythmias, seizures, respiratory depression and death, as well as dependence and withdrawal with chronic use [8, 9]. Although there are risks from use, advocacy groups highlight its potential as a harm reduction tool for opioid withdrawal and use in treatment of conditions such as chronic pain.

Kratom is not scheduled under the Controlled Substances Act (CSA), and the US Food and Drug Administration does not currently recognize it as a lawfully marketed food or dietary supplement, leaving a gap in federal regulation. As a result, regulatory oversight is determined at the state level. State specific regulatory strategies range from a state-wide ban, making it an illegal substance, to being completely unrestricted [10]. Other strategies include state-level Kratom Consumer Protection Acts (KCPA), which aim to reduce harm through measures such as age restrictions and labeling requirements [11]. Many states are considering legislation changes regarding kratom regulation, but research to support the public health impact of such policies is lacking and calls for research to inform regulation have been made [11].

Importance

Kratom use in the United States continues to rise, and legislatures across the country are actively debating the optimal way to regulate its use. There is an urgent public health need for evidence to inform this discussion in a way that promotes safety surrounding kratom use.

Specific aims

The aims of this study include:

1. compare total kratom exposures reported to US poison centers within each state regulatory status;
2. compare rates of severe medical outcomes associated with kratom exposures reported to US poison centers within each state regulatory status;
3. compare rates of kratom exposures resulting in hospitalization within each state regulatory status;
4. compare rates of kratom exposures using healthcare (evaluation at an urgent care, primary care provider, or emergency department or hospitalization) within each state regulatory status; and
5. characterize annual trends, demographic characteristics and clinical characteristics of fatal of kratom-associated exposures reported to US poison centers.

METHODS

Study design and setting

This was a retrospective observational study of kratom exposures reported to the National Poison Data System (NPDS) from 2010 to 2023. The NPDS is a US poisoning data warehouse maintained by America's Poison Center (APC) composed of poisoning exposures reported to the 55 US poison centers, populated with case data in near-real time.

Selection of participants

The NPDS was queried using the APC generic code for kratom from 2010 to 2023. Individuals of all ages were included. Both single and multiple substance exposures were included. Cases coded as 'confirmed non-exposure', representing inquiries regarding suspected kratom exposure that were ultimately determined not to have occurred, were excluded. Cases were categorized by the state from

which the call originated. Reported exposures may represent unique individuals or multiple distinct exposures involving the same individual.

Outcomes

United States poison centers are managed by trained healthcare professionals who assist in managing exposed patients and document the medical care and outcome in a standardized format. Captured data reflect the information provided by the caller at the time of the call. Accuracy of all reported information cannot be verified. Coding standardization is determined by APC. Outcomes of cases are coded as 'no effect', 'minor', 'moderate', 'major' or 'death' according to NPDS medical outcome criteria. Specific medical outcome criteria are available in appendix F of the APC Annual Report [12]. As per NPDS, 'no effect' is when a patient developed no symptoms as a result of exposure. 'Minor effects' refer to symptoms that are minimal with no residual disability (skin irritation, drowsiness and mild gastrointestinal symptoms). 'Moderate effects' are signs or symptoms that are more pronounced, prolonged or of a more systemic nature than minor symptoms, with no residual disability (e.g. fever, disorientation and tachycardia). 'Major effects' are life-threatening or result in residual disability or disfigurement (e.g. coma, hemodynamic collapse, respiratory or cardiac arrest, stroke or status epilepticus). 'Death' is coded when the patient died as a result of or as a direct complication of the exposure or if the exposure was a contributing factor.

The primary outcome was the incidence of severe medical outcomes, defined as cases coded by APC as a major effect or death, within each regulatory status category. A composite outcome was used because deaths alone were infrequently reported and were anticipated to occur at too low a frequency to allow reliable independent analysis, and major effects represent substantial morbidity that regulatory frameworks aim to prevent. Secondary outcomes included incidence of total kratom exposures, kratom exposures resulting in reported healthcare utilization (evaluation by an urgent care, primary care provider, emergency department or hospitalization) and kratom exposures resulting in hospitalization reported to poison centers, stratified by state regulatory status. This was chosen to help identify the total healthcare burden of kratom exposures within each regulatory status. Hospitalization and healthcare utilization categories are not mutually exclusive, as hospitalization represents a subgroup of healthcare utilization. For analysis, any kratom exposure (single substance of polysubstance) that resulted in a poison center contact, healthcare utilization, hospitalization or severe medical outcome was included.

Additional objectives

To aid in characterizing effects associated with kratom toxicity and their possible public health impact, single substance fatalities where kratom was identified as the causative substance, were reported. Fatality narratives for single substance deaths were also analyzed for themes. Information on poison center death causation assessment and documentation is available in Data S1. Themes from deaths with polysubstance exposures were not reported because the death may have been related to a separate substance.

Predictors and covariates of exposure

Outcome predictors were compared across state regulatory classifications. Regulatory status was determined through internet search for each state and the word 'kratom', followed by review of relevant state administrative codes and a summary report from the Legislative Analysis and Public Policy Association (LAPPA) describing kratom laws in all US states [13]. Search was performed by two independent reviewers (G.C. and A.G.). Discrepancies were arbitrated by a third reviewer (R.F.) and a Cohen's κ coefficient is reported for inter-reviewer reliability. States were categorized based on the legislation in effect for at least 50% of the calendar year (i.e. legislation had to be in effect by 1 July to be assigned that category for the year).

Because LAPPA does not provide details regarding timing of the passage of local legislation, local news publications and municipal code were accessed for additional detail. Sources used for the generation of each state legislative category are provided in Data S2. States were grouped by their kratom regulatory status separately for each year into the following four categories: unrestricted, KCPA, local restrictions or banned (Figure 1). States were classified as banned if kratom was listed as a Schedule I substance or if state law explicitly prohibited the sale of kratom. States were classified as having a KCPA if they had age-based sales restrictions, marketing restrictions or quality control requirements regulating product purity and strength. States were classified as having local restrictions if one or more counties or municipalities restricted kratom, but no state-wide regulation was in place. States were classified as unrestricted if no kratom-related regulations existed at either the state or local level.

Analysis and ethical considerations

The number of annual exposures per state was modeled using mixed effects quasi-Poisson regression. The model included year and the state's kratom regulatory status as fixed categorical predictor variables. States were grouped by their kratom regulatory status separately for each year into the following four categories: unrestricted, KCPA, local restrictions if non–state-wide regulation existed or fully banned. The model included an offset term for the log of the state population as reported by census data to account for population size within each group and a state-specific random intercept to account for repeated measures within states.

Exponentiated regression coefficients, interpretable as incidence rate ratios (IRRs), were reported with 95% CI. *Post hoc* comparisons

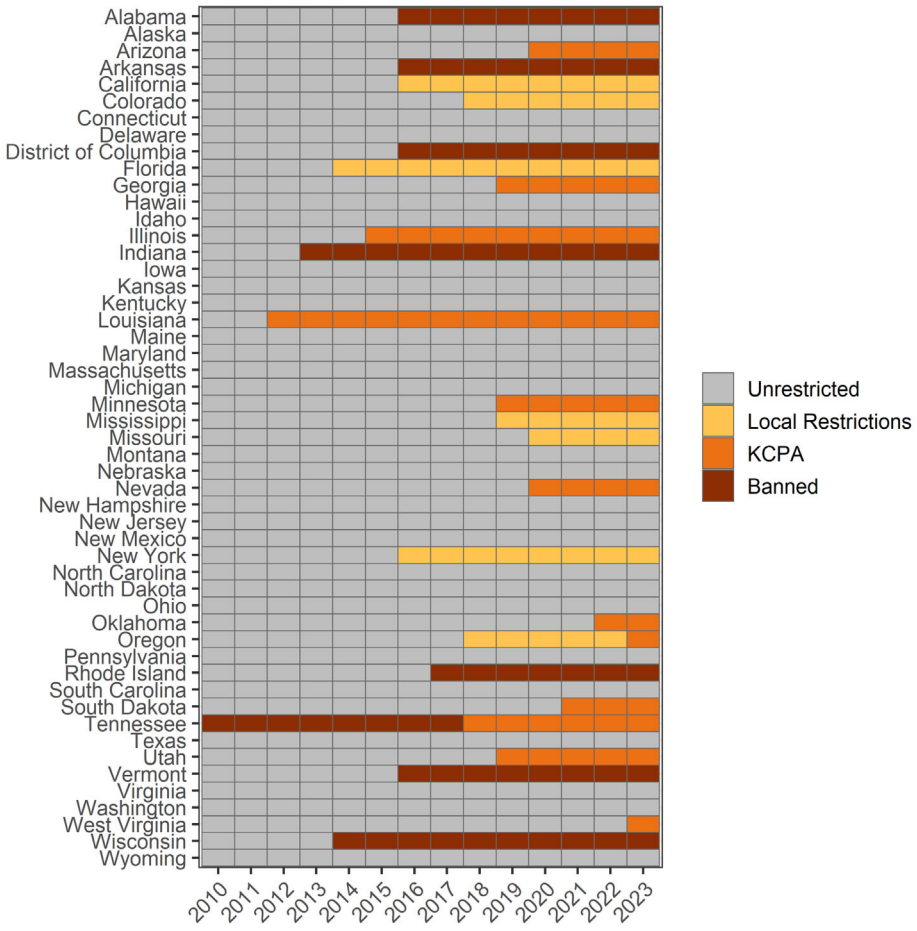


FIGURE 1 Swimmer's plot depicting regulatory status for each state and year.

KCPA= Kratom Consumer Protection Act

were performed to compare rates (averaged over the entire study period) across all pairs of legislative groups, to compare fully banned states with all other jurisdictions, and to assess whether results changed when states or territories with unclear classification status were reclassified [e.g. Disctrict of Columbia (DC)]. a Bonferroni correction was applied to all pairwise comparisons to adjust for multiple testing. Regression results were visualized using a line plot of estimated marginal mean rates over time for each legislative group. The Poisson regression analysis was repeated for the following outcomes: annual exposures resulting in severe outcomes, exposures resulting in hospitalization and exposures resulting in healthcare assessment or hospitalization.

All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, http://www.R-project.org). All tests were two-sided and $P < 0.05$ was considered statistically significant.

Our study protocol was reviewed and judged as non-human subject research by our institutional review board. This manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for reporting observational studies [14]. The research question and analysis plan were not pre-registered on a publicly available platform and results should be considered exploratory.

RESULTS

Characteristics of study subjects

Demographic data is available in Table 1. Of 8919 total exposures, 8411 had an exact age reported, of which the median was 31 years, (IQR = 24–40 years, range = 1 day–100 years), and the majority of cases were male. Pediatric exposures were uncommon with 91% of exposures occurring in adults 18 years and older. States were separated into four categories each year for analysis of annual kratom regulatory status (Figure 1). Inter-rater reliability was excellent (κ = 0.81).

Outcomes by state regulatory status

There was a 65.4-fold increase in kratom-related poison center cases during the study, from 19 cases in 2010 to 1242 cases in 2023 (IRR = 69.0 vs. 2010, 95% CI = 39.6–120, $P < 0.001$). An increase in annual case volume was seen in states of each regulatory category, although the degree of rise differed between regulatory categories (Figure 2). Likewise, incidence of healthcare evaluation, hospitalization and severe medical outcomes associated with kratom rose during the study period, although trends varied by regulatory status. Description

TABLE 1 Patient demographics and characteristics of exposure.

Characteristic	Legislative status				
	Overall *n* = 8919[a]	Unrestricted *n* = 4974[a]	Local restrictions *n* = 2134[a]	KCPA *n* = 1559[a]	Banned *n* = 252[a]
Age, years					
<12	490 (5.5)	259 (5.2)	123 (5.8)	97 (6.2)	11 (4.4)
13–17	205 (2.3)	115 (2.3)	45 (2.1)	41 (2.6)	4 (1.6)
>18	8113 (91)	4537 (91)	1942 (91)	1404 (90)	230 (91)
Unknown age	111 (1.2)	63 (1.3)	24 (1.1)	17 (1.1)	7 (2.8)
Gender					
Female	2736 (31)	1524 (31)	663 (31)	472 (30)	77 (31)
Male	6149 (69)	3425 (69)	1465 (69)	1084 (70)	175 (69)
Unknown	34 (0.4)	25 (0.5)	6 (0.3)	3 (0.2)	0 (0)
Exposure type					
Single substance	5452 (61)	2992 (60)	1419 (66)	880 (56)	161 (64)
Multiple substance	3467 (39)	1982 (40)	715 (34)	679 (44)	91 (36)
Reason					
Intentional—abuse/misuse	5502 (62)	3140 (63)	1292 (61)	905 (58)	165 (65)
Intentional—suspected suicide	1174 (13)	620 (12)	256 (12)	263 (17)	35 (14)
Intentional—unknown	552 (6.2)	313 (6.3)	115 (5.4)	102 (6.5)	22 (8.7)
Other	40 (0.4)	21 (0.4)	13 (0.6)	6 (0.4)	0 (0)
Unintentional	1256 (14)	650 (13)	380 (18)	204 (13)	22 (8.7)
Unknown reason	395 (4.4)	230 (4.6)	78 (3.7)	79 (5.1)	8 (3.2)

Abbreviation: KCPA, Kratom Consumer Protection Act.
[a]*n* (%).

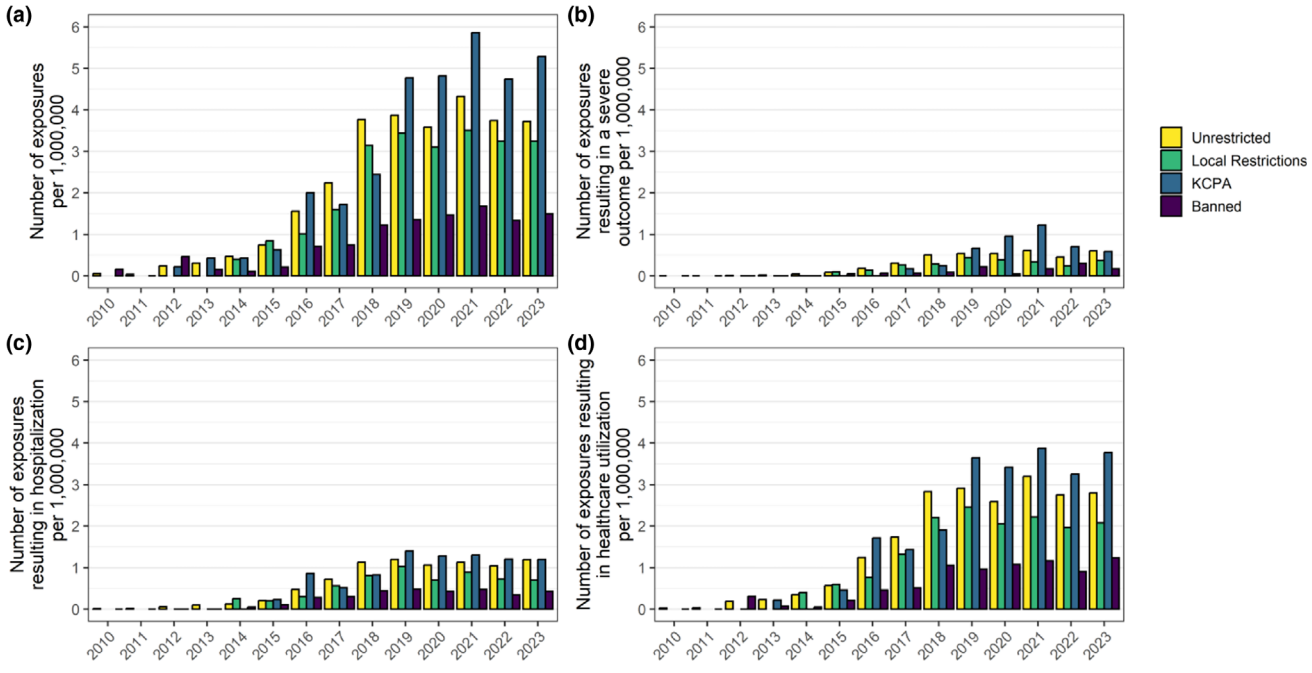
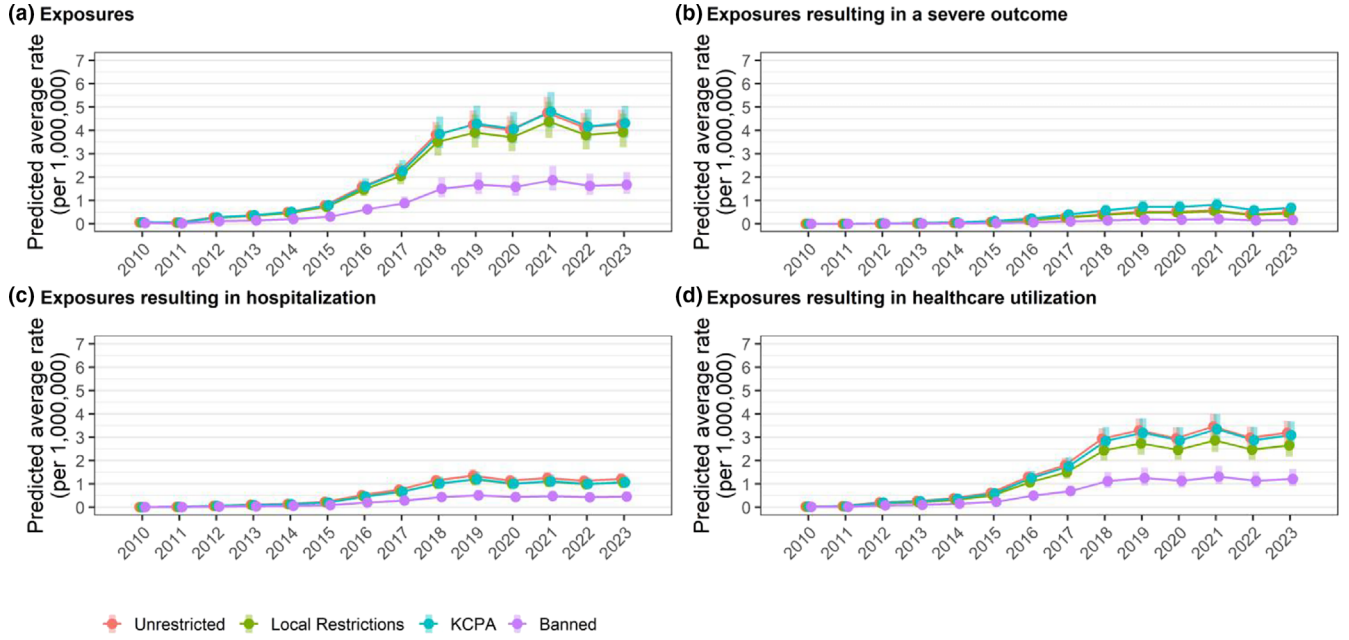


FIGURE 2 Bar chart of (a) annual kratom exposures reported to poison centers, (b) exposure with severe outcomes, (c) exposure with hospitalizations and (d) exposures with healthcare utilization per legislative group.



KCPA= Kratom Consumer Protection Act

FIGURE 3 Estimated marginal mean number (a) annual kratom exposures reported to poison centers, (b) exposure with severe outcomes, (c) exposure with hospitalizations and (d) exposures with healthcare utilization per legislative group modeled using quasi-Poisson regression with an offset for state population.

of patient outcomes and helthcare utilization by regulatory status are available in Table 2. Pairwise contrasts, including 95% CI and *P* values, for the estimated IRRs of each outcome by state regulatory status are presented in Table 3.

There were significantly fewer incidence rates of exposures, severe medical outcomes, healthcare evaluation and hospitalization in states with a ban compared to any other regulatory status (Figure 3, Table 3). Relative to ban states, all other regulatory categories combined were associated with higher incidence rates of poison center-reported exposure (IRR = 2.49, 95% CI = 1.89–3.28), severe outcomes (IRR = 3.19, 95% CI = 1.78–5.70), healthcare evaluation (IRR = 2.44, 95% CI = 1.66–3.60) and hospitalization (IRR = 2.45, 95% CI = 1.81–3.30; all $P < 0.001$). States with no kratom regulation (unrestricted) also demonstrated higher incidence rates of healthcare utilization compared with states with at least local restrictions in place (IRR = 1.20, 95% CI = 1.02–1.42), although this difference did not reach statistical significance ($P = 0.168$). No significant differences were observed between other regulatory categories (KCPA vs. local restriction; KCPA vs. unrestricted). Pairwise comparisons between regulatory classifications, reported as IRRs for each outcome, and each year, are available in Data S3.

Patient outcomes

The majority of kratom exposures (72.5%) received evaluation in healthcare settings (Table 2). Hospitalization occurred in 3035 cases (34%). Of those requiring hospital admission, 1353 (44.5%) were admitted to critical care units. Comparatively fewer single-substance kratom exposures required healthcare evaluation, hospitalization or critical care admission.

Among all kratom exposures, there were 174 deaths (2%), and 27 were reported among single substance kratom exposures (0.5%) (Table 2). Two deaths occurred in adolescent patients, both were polysubstance exposures. No deaths in children 12 years or younger were reported. Severe medical outcomes, defined as either death or major effects, were documented more frequently in polysubstance exposures (13%) as compared to single substances exposures (8.7%).

In the 490 kratom exposures in children less than or equal to 12 years, 163 (33%) were evaluated in a healthcare facility, 32 (6.5%) were admitted to a hospital and 11 (2.2%) were admitted to critical care units. Two (0.4%) children 12 years and younger experienced major medical effects, and there were no deaths. In one, a 2-day-old male experienced tremor, tachycardia, bradycardia and hyperventilation. In the other, a 22-month-old male experienced agitation and major central nervous system depression.

Of the single substance kratom deaths, six cases were adjudicated as 'probably' or 'undoubtedly responsible,' five involved males younger than 30 years of age. These individuals were found in cardiac arrest or were found unresponsive and subsequently developed cardiac arrest, all with a documented history of kratom use or recent ingestion. Care was withdrawn within days because of severe anoxic brain injury. No clear prodromal symptoms were described in four of the five cases. In one case, a kratom user experienced a seizure during

TABLE 2 Description of patient outcomes and characterization of healthcare utilization.

Characteristic	Legislative status				
	Overall *n* = 8919[a]	Unrestricted *n* = 4974r[a]	Local restrictions *n* = 2134[a]	KCPA *n* = 1559[a]	Banned *n* = 252[a]
Health care utilization					
Critical care	1353 (15.2)	810 (16.3)	285 (13.4)	207 (13.3)	51 (20.2)
Non-critical care	1141 (12.8)	657 (13.2)	259 (12.1)	196 (12.6)	29 (11.5)
Psychiatric facility	541 (6.1)	308 (6.2)	89 (4.2)	131 (8.4)	13 (5.2)
Treated/evaluated and released	3432 (38.5)	1956 (39.3)	805 (37.7)	580 (37.2)	91 (36.1)
Patient lost to follow-up or left AMA	936 (10.5)	461 (9.3)	276 (12.9)	166 (10.6)	33 (13.1)
Patient refused referral or did not arrive	309 (3.5)	175 (3.5)	76 (3.6)	46 (3.0)	12 (4.8)
No healthcare evaluation was reported or recommended	1207 (13.5)	607 (12.2)	344 (16.1)	233 (14.9)	23 (9.1)
Clinical outcome					
Death	174 (2.0)	74 (1.5)	21 (1.0)	76 (4.9)	3 (1.2)
Major effect	979 (11)	589 (12)	212 (9.9)	153 (9.8)	25 (9.9)
Moderate effect	3325 (37)	2022 (41)	665 (31)	536 (34)	102 (40)
Minor effect	1838 (21)	922 (19)	476 (22)	381 (24)	59 (23)
No effect	607 (6.8)	336 (6.8)	127 (6.0)	128 (8.2)	16 (6.3)
Not followed, minimal effects	721 (8.1)	383 (7.7)	237 (11)	85 (5.5)	16 (6.3)
Not followed, judged as nontoxic	28 (0.3)	9 (0.2)	15 (0.7)	4 (0.3)	0 (0)
Unable to follow, judged as a potentially toxic	1005 (11)	496 (10.0)	324 (15)	161 (10)	24 (9.5)
Unrelated effect	242 (2.7)	143 (2.9)	57 (2.7)	35 (2.2)	7 (2.8)

Subgroup of single substance exposures

Characteristic	Legislative status				
	n = 5452[a]	*n* = 2992[a]	*n* = 1419[a]	*n* = 880[a]	*n* = 161[a]
Health care utilization					
Critical care	559 (10.3)	332 (11.1)	130 (9.2)	78 (8.9)	19 (11.8)
Noncritical care	560 (10.3)	312 (10.4)	142 (10.0)	95 (10.8)	11 (6.8)
Psychiatric facility	194 (3.6)	109 (3.6)	33 (2.3)	44 (5.0)	8 (5.0)
Treated/evaluated and released	2315 (42.5)	1307 (43.7)	576 (40.6)	363 (41.3)	69 (42.9)
Patient lost to follow-up or left AMA	674 (12.4)	318 (10.6)	213 (15.0)	118 (13.4)	25 (15.5)
Patient refused referral or did not arrive	234 (4.3)	130 (4.3)	63 (4.4)	34 (3.9)	7 (4.3)
No healthcare evaluation was reported or recommended	916 (16.8)	484 (16.2)	262 (18.5)	148 (16.8)	22 (13.7)
Clinical outcome					
Death	27 (0.5)	15 (0.5)	4 (0.3)	7 (0.8)	1 (0.6)
Major effect	446 (8.2)	256 (8.6)	107 (7.5)	70 (8.0)	13 (8.1)
Moderate effect	1,820 (33)	1,075 (36)	422 (30)	264 (30)	59 (37)
Minor effect	1,185 (22)	601 (20)	313 (22)	231 (26)	40 (25)
No effect	440 (8.1)	264 (8.8)	80 (5.6)	82 (9.3)	14 (8.7)
Not followed, minimal effects	569 (10)	306 (10)	179 (13)	72 (8.2)	12 (7.5)
Not followed, judged as nontoxic	24 (0.4)	8 (0.3)	12 (0.8)	4 (0.5)	0 (0)
Unable to follow, judged as a potentially toxic	751 (14)	364 (12)	252 (18)	119 (14)	16 (9.9)
Unrelated effect	190 (3.5)	103 (3.4)	50 (3.5)	31 (3.5)	6 (3.7)

Abbreviations: AMA, Against Medical Advice; KCPA, Kratom Consumer Protection Act.
[a]*n* (%).

TABLE 3 *Post-hoc* contrasts from each quasi-Poisson regression model, comparing all pairs of state regulatory statuses.

	Incidence rate ratio [95% CI] for outcome			
	Exposure	**Exposures resulting in a severe outcome**	**Exposures resulting in hospitalization**	**Exposures resulting in healthcare assessment or hospitalization**
Unrestricted vs. banned	**2.548 [1.929–3.366] *P* < 0.001**	**2.890 [1.614–5.176] *P* = 0.002**	**2.659 [1.800–3.927] *P* < 0.001**	**2.629 [1.947–3.548] *P* < 0.001**
Local restrictions vs. banned	**2.347 [1.731–3.182] *P* < 0.001**	**2.711 [1.415–5.196] *P* = 0.016**	**2.334 [1.511–3.606] *P* < 0.001**	**2.183 [1.571–3.033] *P* < 0.001**
KCPA vs. banned	**2.574 [1.927–3.439] *P* < 0.001**	**4.130 [2.239–7.620] *P* < 0.001**	**2.344 [1.552–3.540] *P* < 0.001**	**2.546 [1.863–3.481] *P* < 0.001**
KCPA, local restrictions, or unrestricted vs. banned	**2.488 [1.885–3.282] *P* < 0.001**	**3.187 [1.783–5.695] *P* < 0.001**	**2.441 [1.655–3.602] *P* < 0.001**	**2.445 [1.813–3.296] *P* < 0.001**
Unrestricted vs. local restrictions	1.085 [0.933–1.263] *P* = 1.000	1.066 [0.738–1.539] *P* = 1.000	1.139 [0.901–1.441] *P* = 1.000	**1.204 [1.020–1.421] *P* = 0.168**
Unrestricted vs. KCPA	0.990 [0.869–1.127] *P* = 1.000	0.700 [0.527–0.929] *P* = 0.082	1.134 [0.927–1.389] *P* = 1.000	1.032 [0.895–1.191] *P* = 1.000
Local restrictions vs. KCPA	0.912 [0.766–1.086] *P* = 1.000	0.656 [0.438–0.985] *P* = 0.251	0.996 [0.755–1.313] *P* = 1.000	0.857 [0.707–1.039] *P* = 0.698

Notes: The exponentiated regression estimates (interpreted as incidence rate ratios) are presented with 95% CI. *P*-values were adjusted using a Bonferroni correction for each regression model. Comparisons between all regulatory classes for each year and outcome can be found in Data S3. Bolded values represent those with 95% CI of incidence rate ratio > 1.
Abbreviation: KCPA, Kratom Consumer Protection Act.

intercourse, prompting emergency medical services, who subsequently found the patient in cardiac arrest. The sixth case involved a woman in her 50s who became unresponsive following kratom ingestion. She aspirated and required intubation, with subsequent concern for secondary sepsis. She developed hypotension and multi-system organ failure and died 3 days later. Confirmatory mitragynine concentrations were obtained in two of the six cases to corroborate kratom exposure.

DISCUSSION

Our study demonstrates a significant increase in kratom exposures reported to US poison centers over the past decade, consistent with previously published trends. [15] Alongside this rise, incidence rates of reported severe clinical effects and subsequent healthcare utilization have also increased. Although some exposures may have no adverse effects, severe effects such as seizure, coma and cardiac arrest are reported in this study. Nearly one in seven cases reported to a poison center with a single-substance kratom exposures were admitted to a hospital, and one in 16 were admitted to a critical care unit, highlighting the potential severity of kratom toxicity.

Although severe medical outcomes were common, it is important to recognize that prior studies have shown kratom is frequently used in combination with other psychoactive substances. For example, Olsen *et al.* [16] reported that among 152 decedents who tested positive for mitragynine *post-mortem*, only seven had no other psychoactive substances detected, and fentanyl was the most frequently listed cause of death [16]. More recent cases, however, have documented and increasing number of fatalities attributed to kratom use alone [17].

There are multiple mechanisms by which kratom can produce acute toxicity, including but not limited to hepatotoxicity, risk for cardiac dysrhythmia and seizure risk [18–20]. Although pre-clinical data suggest decreased risk for respiratory depression when compared with traditional opioids, cases of respiratory depression responsive to naloxone in patients without co-exposure to opioids has been reported [21]. Additionally, kratom is known to interact with P-glycoprotein as well as cytochrome P450 enzymes 2D6 and 3A4, potentially increasing the risk of adverse outcomes when used concurrently with other substances [17, 22]. Given the common practice of polysubstance use among kratom users, its safety profile and potential role as a harm reduction agent remain questionable.

As states continue to evaluate kratom legislation, our findings suggest that regulatory approaches short of an outright ban were not associated with lower rates of exposure, healthcare utilization or severe outcomes when compared to unrestricted states. In contrast, rates were consistently lower in states with kratom ban in place. These findings are consistent with prior studies showing lower incidence of kratom use in states with bans and no corresponding reduction in states with KCPA legislation [23].

Several hypotheses may explain these patterns. Availability of kratom is widespread among states without bans, irrespective of the presence of regulation [24]. Bans may reduce the availability of kratom in retail settings and its visibility through advertising, potentially decreasing both access and awareness. Although these findings do not establish causality, they raise important questions about the effectiveness of consumer protection-focused legislative framework.

The broader public health implications of kratom bans, including substance abuse patterns or management of withdrawal, are unclear. Legislators must navigate these questions without access to high-

quality evidence to inform decisions. Additionally, a portion of the limited literature available to inform decision-making has been published by groups with industry affiliations [4, 11]. There is an urgent need for larger, methodologically rigorous investigation independent of special group interest to better characterize benefits and risks of kratom access.

Kratom regulatory responsibility fell to states in 2016 following the withdrawal of a 2016 Drug Enforcement Agency (DEA) proposal to schedule mitragynine and 7-hydroxymitragynine [25]. At present, no federal approval or oversight mechanism exists, despite the DEA listing kratom as a drug of concern [26]. The US Food and Drug Administration kratom website as of 2025 states that it is not safe or lawful as a dietary supplement or food additive, and it cannot be legally added to dietary supplements or conventional foods [11, 26]. The resulting heterogeneity of state regulation has resulted in a rapidly evolving and inconsistent regulatory landscape.

State lawmakers continue to debate and explore legislation. Since the beginning of 2023, five of the six states with kratom bans have introduced or are considering KCPA legislation. Rhode Island passed a bill to implement a KCPA through both chambers of state congress, although it was ultimately vetoed. Florida passed a KPCA in 2023, Maryland in 2024, with Nebraska and South Carolina passing regulatory legislation in 2025 [13]. Debates continue in statehouses elsewhere, with South Dakota, Connecticut, Hawaii, Illinois, Missouri and New York exploring regulatory frameworks or legislation, which would classify kratom as a controlled substance [13].

Our findings highlight the need for high-quality data to continue to inform this ongoing policy debate. Future research should continue to rigorously evaluate public health outcomes associated with different regulatory frameworks to support evidence-based legislative and public health decisions.

Limitations

These findings are subject to important limitations. First is the inherent limitation of retrospective reviews because of potential for confounding. We, therefore, emphasize that any relationships between incidence rates and state regulatory status should be viewed as association rather than a causal link. Because polysubstance exposures were included, adverse outcomes and healthcare utilization may not be attributable solely to kratom. Toxicity from co-ingested substances may have been the primary driver, with kratom functioning as a contributing or non-relevant exposure.

We assessed the impact of KCPAs as a heterogeneous group of interventions. It is possible that specific regulatory components within this bundle exerted meaningful effects that were not detected because they were grouped with less effective measures. Accurately characterizing the legal and regulatory status of kratom across US states is inherently challenging because of variability in statutory language, administrative codes and the evolving nature of state and local regulations. As a result, some degree of state-level misclassification cannot be entirely excluded.

Certain jurisdictions, such as the District of Columbia, were particularly difficult to classify because of conflicting statutory and regulatory interpretations regarding the scheduling of kratom and its alkaloids [13]. However, given our findings, any misclassification would most likely bias results toward a type II error. For example, classifying jurisdictions with conflicting legislation as having a ban would tend to inflate exposure counts in 'banned' states, thereby attenuating observed effects. *Post hoc* sensitivity analyses were performed for jurisdictions such as the District of Columbia, and results were unchanged by reclassification. Finally, the sources and methods used for regulatory classification are fully described, allowing the analysis to be replicated or reclassified as appropriate.

Another important limitation is the inherent nature of poison center data, which rely on passive reporting. Poison centers depend on information provided by callers and are unable to independently confirm the specific substances reported. Laboratory confirmation of kratom exposure in clinical practice is exceedingly rare, consequently, most cases are evaluated and managed based on patient report. Additionally, because poison center data are encounter-based rather than patient-based, individuals may contribute more than one exposure, and the inability to reliably link repeat encounters precluded adjustment for within-person correlation.

Finally, poison center data is not representative of population incidence data. However, prior analyses suggest these data reflect similar trends observed in larger national databases, albeit on a smaller scale. For instance, the 2022 APC annual report demonstrated that rates of fentanyl exposures with serious outcomes rose at the same rate as Centers for Disease Control and Prevention None. Wide-ranging ONline Data for Epidemiologic Research (CDC WONDER) fentanyl fatality data [27].

No single database is likely able to capture the public health impacts related to kratom. Poison center data have the advantage of including cases from individuals who did not seek healthcare, but are limited by passive reporting nature and cannot log an exposure if not contacted. In contrast, healthcare aggregate data depend on proper coding and accurate identification of kratom as a contributing health issue. Under-reporting is a concern no matter the data source, as mitragynine testing is not routine. Notably, under-reporting may be further exacerbated in states with kratom bans, where individuals may be reluctant to contact poison centers or seek medical care because of fear of potential legal consequences.

CONCLUSION

Our study highlights the increasing public health concerns associated with kratom, evidenced by a significant rise in poison center-reported exposures and severe medical outcomes over the past decade. States with bans experienced a lower incidence of severe kratom-related medical outcomes and healthcare utilization. Conversely, states with consumer protections acts designed to promote safety experienced similar rates of severe outcomes as states with no regulation at all. These findings may help inform legislators of the possible health

effects of widespread kratom availability, but do not assess unintended consequence of kratom not being available.

AUTHOR CONTRIBUTIONS

Grant Comstock: Conceptualization; investigation; writing—original draft; methodology; writing—review and editing. **Anthony P. Gulotta:** Investigation; data curation; writing—original draft; project administration; validation. **Lisa E. Rein:** Formal analysis; software. **Ryan Feldman:** Conceptualization; investigation; writing—original draft; methodology; writing—review and editing; project administration; data curation.

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DECLARATION OF INTERESTS

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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