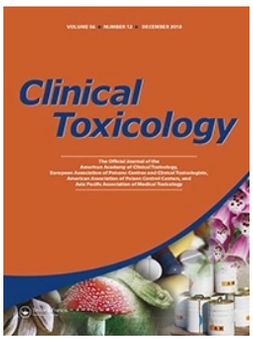

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POISON CENTRE RESEARCH

Kratom exposures reported to United States poison control centers: 2011–2017

Sara Post[a,b], Henry A. Spiller[c,d], Thitphalak Chounthirath[a] and Gary A. Smith[a,d,e]

[a]Center for Injury Research and Policy, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA; [b]Northeast Ohio Medical University, Rootstown, OH, USA; [c]Central Ohio Poison Center, Columbus, OH, USA; [d]Department of Pediatrics, College of Medicine, The Ohio State University, Columbus, OH, USA; [e]Child Injury Prevention Alliance, Columbus, OH, USA

ABSTRACT

Context: Kratom, or *Mitragyna speciosa*, is a plant indigenous to Southeast Asia that has gained national attention in the United States for its increased use in the self-management of opioid withdrawal and pain, as well as for concerns about its safety.

Methods: This study analyzes exposures to kratom reported to poison control centers (PCCs) in the United States during 2011–2017 from the National Poison Data System (NPDS).

Discussion: From 2011 through 2017, 1807 kratom exposures were reported to United States PCCs. Almost two-thirds (65.0%) of these exposures occurred during 2016–2017. Most exposures occurred among adults ≥20 years (88.9%), males (70.8%), at a residence (86.1%), and were intentional (74.3%). Among first-ranked kratom exposures, 31.8% resulted in admission to a health care facility (HCF) and 51.9% in a serious medical outcome. Multiple-substance exposures were associated with greater odds of admission to a HCF (OR: 2.80; 95% CI: 2.21–3.55) and a serious medical outcome (OR: 2.25; 95% CI: 1.77–2.85) compared with single-substance exposures. There were 11 deaths associated with kratom exposure, including two that occurred after exposure to kratom only. Among kratom-only exposures, 86.1% resulted in one or more clinical effects. The most common clinical effects were agitation/irritability (22.9%) and tachycardia (21.4%). There were seven neonatal exposures, including five experiencing withdrawal.

Conclusions: Kratom is associated with a variety of serious medical outcomes, especially when used with other substances. More research is needed to define the human response to kratom. Increased regulation of kratom products would help guarantee product quality and safety. Individuals who choose to use kratom should be educated about its potential risks, including the dangers of using it in combination with other substances.

Abbreviations: AAPCC: American Association of Poison Control Centers; CI: Confidence Interval; CCU: Critical Care Unit; DEA: Drug Enforcement Administration; FDA: Food and Drug Administration; HCF: Health Care Facility; NPDS: National Poison Data System; OR: Odds Ratio; PCC: Poison Control Center; US: United States

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Kratom; poison control center; National Poison Data System; dietary supplement; poisoning

Introduction

Kratom, a plant indigenous to Southeast Asia, has recently gained national attention in the United States (US) for its increasing use in the self-management of opioid withdrawal and pain, as well as for concerns about its safety [1]. The leaves of kratom, or *Mitragyna speciosa,* have been widely used for centuries in Southeast Asia for pain management and withdrawal from opium, typically by ingesting raw leaves or consuming teas made using the leaves. Kratom leaves are reported to produce mild stimulant effects at low to moderate doses (1–5 g), opioid-like effects at moderate to high doses (5–15 g), and sedative effects at very high doses (>15 g) [2]. With increased use of kratom products in the US, the number of exposures reported to US poison control centers (PCCs) increased tenfold from 2010 to 2015 [3]. In addition, there has been an increase in reported adverse effects associated with kratom, which prompted the Drug Enforcement Administration (DEA) to consider classifying kratom as a Schedule I drug, and the Food and Drug Administration (FDA) to warn consumers against its use [4,5]. Kratom is listed by the DEA as a "drug of concern" and has not been approved for any medical use by the FDA [6].

A number of studies have sought to elucidate the pharmacologic properties of kratom or surveyed kratom users [1,2,7–10], but comparatively few have assessed the epidemiology of its use or abuse [3,7,11]. One study evaluated 15 kratom exposures reported to PCCs and reported clinical effects that included altered mental status, agitation, CNS depression, seizures, and tachycardia [11]. Intrahepatic cholestasis and symptoms of dependence and withdrawal with repeated kratom consumption have also been reported [12,13]. There have been reports of death associated with kratom use, but the majority occurred in combination with use of other drugs, including prescription opioids and benzodiazepines [14]. Another brief report described kratom exposures reported to US PCCs from 2010 to 2015 [3]. This study

CONTACT Gary A. Smith gary.smith@nationwidechildrens.org Center for Injury Research and Policy, The Research Institute at Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA

utilized data from the National Poison Data System (NPDS) database from 2011 to 2017 to investigate exposures to kratom reported to US PCCs. This study provides a more in-depth analysis of kratom exposures than previous reports, and because of the rapid increase in exposures since 2015, provides an important update to our understanding of the characteristics and secular trends of kratom use.

Methods

Data sources and study design

Kratom exposure data were obtained and retrospectively analyzed from the NPDS, a database owned and maintained by the American Association of Poison Control Centers (AAPCC). The NPDS receives data submitted by AAPCC member PCCs regarding calls received through the Poison Help Line [15].

Case selection criteria

The NPDS was queried for reported kratom exposures among individuals of all ages from January 1, 2011 through December 31, 2017 using the AAPCC's product codes for "Plants-*Mitragyna*" or "*Mitragyna speciosa* korthals (botanic name)" and the generic code for "Kratom" in cases with a missing product code. Both single-substance and multiple-substance exposures involving kratom were included, though only single-substance exposures were used in the analysis of clinical effects. Cases were excluded if a) the medical outcome was "confirmed non-exposure" or "unrelated effect, the exposure was probably not responsible for the effect(s)," or b) the exposure occurred outside of the 50 US states or District of Columbia.

Variables

Age groups were designated as children ($\leq$12 years), adolescents (13–19 years), and adults ($\geq$20 years). Reason for exposure was categorized as unintentional, intentional, adverse reaction, other, and unknown. Intentional reasons were subcategorized into suspected suicide, abuse or misuse, and unknown. Exposure site was grouped into residence (own or other), other, and unknown.

Level of care received was categorized as no health care facility (HCF) care received; treated and released; admission to a HCF, including to a critical care unit (CCU), non-CCU, or psychiatric facility; or other (patient refused referral, did not arrive at the HCF, was lost to follow-up, or left against medical advice). Medical outcomes were grouped into serious (including death, major effect, and moderate effect), minor effect, no effect, not followed (at most minimal clinical effect expected), or unable to follow. As defined by the NPDS, major effects are life-threatening or result in significant residual disability or disfigurement. Moderate effects are more pronounced, prolonged or systemic compared with minor effects, and involve some form of indicated treatment. Minor effects are minimally bothersome and usually resolve rapidly [15].

Because of the paucity of information about the clinical effects associated with kratom exposure in humans, clinical effects were included if they were classified as "related" or "unknown if related" to the exposure. Other variables included in this study were year of exposure, product form, and route of exposure.

Statistical analysis and ethical considerations

IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY) and SAS Enterprise Guide 7.15 (SAS Institute Inc., Cary, NC) software were used to conduct data analysis. All single-substance and multiple-substance exposures were used to analyze exposure trends and the general characteristics of kratom exposures, including age, gender, reason of exposure, exposure site, and route of exposure. When multiple substances are involved in an exposure, the PCC specialist ranks the substances in the order each is judged to have contributed to the individual's clinical effects with the first-ranked substance being the most likely to account for the observed effects. For simplicity, the term "first-ranked kratom exposure" will be used in this article to refer to exposures where the first-ranked substance was kratom. Management site, level of HCF care received, and medical outcome was analyzed using only first-ranked kratom exposures (including single-substance exposures). Clinical effects and therapy received were analyzed using only single-substance exposures to avoid possible substance interactions that may occur among multiple-substance exposures. However, among the seven neonatal cases, clinical effects were reported for both single-substance and first-ranked kratom exposures. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The institutional review board at the authors' institution judged this study as exempt.

Results

General characteristics, exposure rates, and trends

A total of 1807 single-substance (65.0%) and multiple-substance (35.0%) exposures involving kratom were reported to US PCCs during 2011–2017, with 65.0% of these exposures occurring in 2016–2017. Almost all exposures (96.5%) occurred among adults $\geq$20 years (88.9%) and adolescents (7.6%). The mean age of individuals exposed to kratom was 31.2 years (SD = 12.2, median = 29.0 years, interquartile range = 23.0–38.0 years). Males accounted for a majority of all exposures (70.8%), and across age groups (Table 1). The majority of exposures occurred at a residence (86.1%) and was intentional (74.3%). The most common routes of exposure were ingestion alone (82.7%) or ingestion with other routes (5.0%), followed by nasal inhalation (3.6%).

The annual number of exposures increased by 52.5-fold, from 13 exposures in 2011 to 682 exposures in 2017 (Figure 1). From 2011 through 2017, the annual exposure rate per million US residents increased by 58.1-fold among

Table 1. Characteristics of single-substance and multiple-substance kratom exposures by age group, NPDS 2011–2017.

Characteristics	≤12 years *n* (%[a])	13–19 years *n* (%[a])	≥20 years *n* (%[a])	Unknown *n* (%[a])	Total *n* (%[a])
Type of exposure					
Single-substance	42 (87.5)	80 (58.4)	1039 (64.7)	13 (86.7)	1174 (65.0)
Multiple-substance	6 (12.5)	57 (41.6)	568 (35.3)	2 (13.3)	633 (35.0)
Gender					
Male	28 (58.3)	107 (78.1)	1136 (70.7)	8 (53.3)	1279 (70.8)
Female	20 (41.7)	30 (21.9)	464 (28.9)	5 (33.3)	519 (28.7)
Unknown	0 (0.0)	0 (0.0)	7 (0.4)	2 (13.3)	9 (0.5)
Chronicity					
Acute	39 (81.3)	103 (75.2)	918 (57.1)	8 (53.3)	1068 (59.1)
Chronic	7 (14.6)	10 (7.3)	296 (18.4)	3 (20.0)	316 (17.5)
Acute-on-chronic	1 (2.1)	7 (5.1)	224 (13.9)	0 (0.0)	232 (12.8)
Unknown	1 (2.1)	17 (12.4)	169 (10.5)	4 (26.7)	191 (10.6)
Exposure site					
Residence	42 (87.5)	104 (75.9)	1400 (87.1)	10 (66.7)	1556 (86.1)
Other	5 (10.4)	18 (13.1)	101 (6.3)	1 (6.7)	125 (6.9)
Unknown	1 (2.1)	15 (10.9)	106 (6.6)	4 (26.7)	126 (7.0)
Reason					
Intentional	2 (4.2)	120 (87.6)	1209 (75.2)	11 (73.3)	1342 (74.3)
Abuse/misuse	2 (4.2)	104 (75.9)	962 (59.9)	10 (66.7)	1078 (59.7)
Suspected suicide	0 (0.0)	14 (10.2)	149 (9.3)	0 (0.0)	163 (9.0)
Unknown	0 (0.0)	2 (1.5)	98 (6.1)	1 (6.7)	101 (5.6)
Unintentional	39 (81.3)	4 (2.9)	128 (8.0)	1 (6.7)	172 (9.5)
Adverse reaction	0 (0.0)	5 (3.6)	135 (8.4)	0 (0.0)	140 (7.7)
Other	6 (12.5)	3 (2.2)	90 (5.6)	1 (6.7)	100 (5.5)
Unknown	1 (2.1)	5 (3.6)	45 (2.8)	2 (13.3)	53 (2.9)
Exposure route					
Ingestion	38 (79.2)	113 (82.5)	1337 (83.2)	11 (73.3)	1499 (83.0)
Ingestion with other routes	2 (4.2)	12 (8.8)	77 (4.8)	0 (0.0)	91 (5.0)
Nasal inhalation	1 (2.1)	5 (3.6)	59 (3.7)	0 (0.0)	65 (3.6)
Other[b]	6 (12.5)	1 (0.7)	18 (1.1)	0 (0.0)	25 (1.4)
Unknown	1 (2.1)	6 (4.4)	116 (7.2)	4 (26.7)	127 (7.0)
Total (row %[c])	48 (2.7)	137 (7.6)	1607 (88.9)	15 (0.8)	1807 (100.0)

[a]Column and [c]row percentages may not sum to 100.0% because of rounding error.
[b]Includes other single or multiple routes.

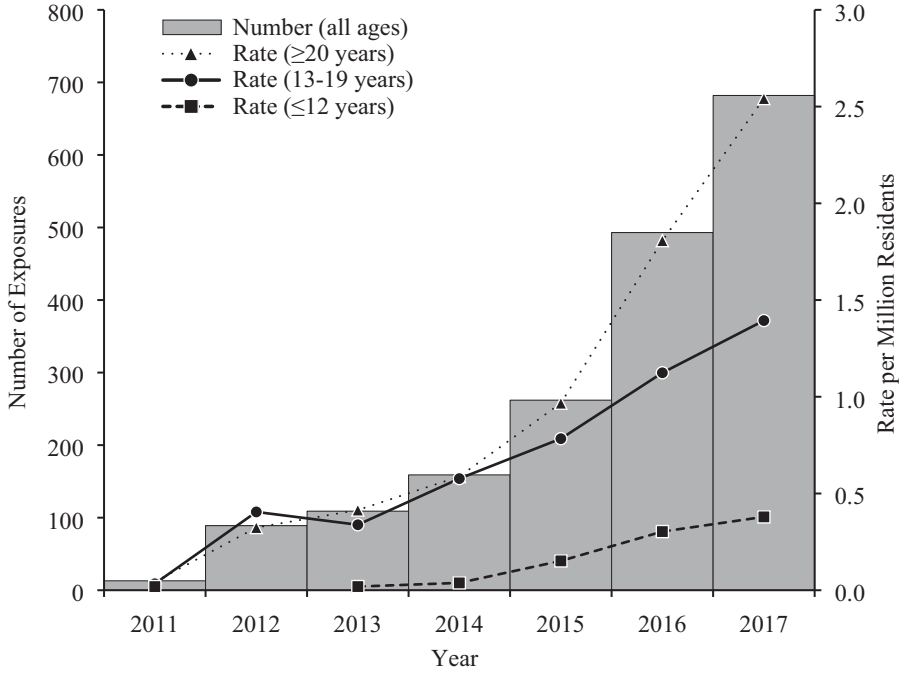

Figure 1. Annual number and rate of single-substance and multiple-substance kratom exposures by age group, NPDS 2011–2017.

adults, 41.7-fold among adolescents and 20.1-fold among children. Exposure rates per million state residents were highest in Idaho (3.9) and Oregon (3.8) and lowest in Delaware (0.2) and Wisconsin (0.2) (Figure 2).

Management site, HCF level of care received, and medical outcome

There were 1566 first-ranked kratom exposures. Of these, only 9.2% of the exposures were managed on-site at a non-

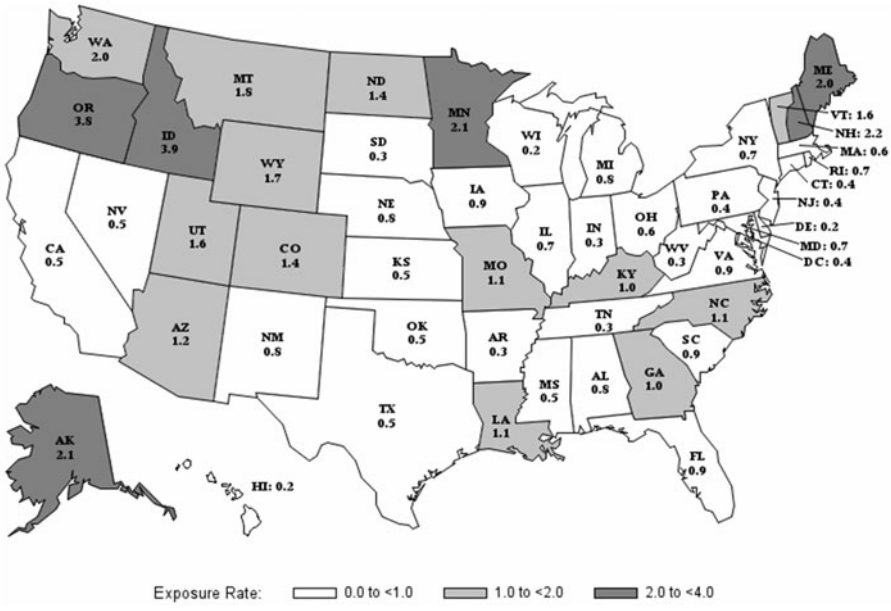

Figure 2. Kratom exposure rate per million state residents by state, NPDS 2011–2017.

Table 2. Management site, Level of care received, and medical outcome associated with First-Ranked kratom exposures by exposure type and age group, NPDS 2011–2017.

		Single-substance exposures				Multiple-substance exposures			
Characteristics	Study total[a] *n* (%[b])	≤12 Years *n* (%[b])	13–19 Years *n* (%[b])	≥20 Years *n* (%[b])	Subtotal[a] *n* (%[b])	≤12 Years *n* (%[b])	13–19 Years *n* (%[b])	≥20 Years *n* (%[b])	Subtotal[a] *n* (%[b])
Management site									
Patient already in (enroute to) a HCF when PCC called	1240 (79.2)	11 (26.2)	57 (71.3)	825 (79.4)	898 (76.5)	3 (100.0)	29 (78.4)	310 (88.1)	342 (87.2)
Patient was referred by PCC to a HCF	154 (9.8)	9 (21.4)	12 (15.0)	96 (9.2)	120 (10.2)	0 (0.0)	6 (16.2)	28 (8.0)	34 (8.7)
Managed on-site (non-HCF)	144 (9.2)	21 (50.0)	9 (11.3)	96 (9.2)	131 (11.2)	0 (0.0)	2 (5.4)	11 (3.1)	13 (3.3)
Other	18 (1.1)	1 (2.4)	1 (1.3)	14 (1.3)	16 (1.4)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.5)
Unknown	10 (0.6)	0 (0.0)	1 (1.3)	8 (0.8)	9 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Level of care received									
No HCF treatment received	172 (11.0)	22 (52.4)	11 (13.8)	118 (11.4)	156 (13.3)	0 (0.0)	2 (5.4)	14 (4.0)	16 (4.1)
Treated/evaluated and released	696 (44.4)	8 (19.0)	42 (52.5)	510 (49.1)	561 (47.8)	0 (0.0)	9 (24.3)	126 (35.8)	135 (34.4)
Admitted	498 (31.8)	6 (14.3)	17 (21.3)	281 (27.0)	304 (25.9)	3 (100.0)	22 (59.5)	169 (48.0)	194 (49.5)
Admitted to a critical care unit	219 (14.0)	2 (4.8)	4 (5.0)	113 (10.9)	119 (10.1)	1 (33.3)	14 (37.8)	85 (24.1)	100 (25.5)
Admitted to a non-critical care unit	205 (13.1)	4 (9.5)	7 (8.8)	128 (12.3)	139 (11.8)	2 (66.7)	4 (10.8)	60 (17.0)	66 (16.8)
Admitted to a psychiatric facility	74 (4.7)	0 (0.0)	6 (7.5)	40 (3.8)	46 (3.9)	0 (0.0)	4 (10.8)	24 (6.8)	28 (7.1)
Patient refused referral/did not arrive at HCF	47 (3.0)	2 (4.8)	2 (2.5)	31 (3.0)	35 (3.0)	0 (0.0)	0 (0.0)	12 (3.4)	12 (3.1)
Patient lost to follow-up/left against medical advice	153 (9.8)	4 (9.5)	8 (10.0)	99 (9.5)	118 (10.1)	0 (0.0)	4 (10.8)	31 (8.8)	35 (8.9)
Medical outcome									
No effect	90 (5.7)	17 (40.5)	4 (5.0)	57 (5.5)	80 (6.8)	0 (0.0)	0 (0.0)	10 (2.8)	10 (2.6)
Minor effect	372 (23.8)	4 (9.5)	26 (32.5)	260 (25.0)	294 (25.0)	1 (33.3)	11 (29.7)	66 (18.8)	78 (19.9)
Serious outcome	813 (51.9)	2 (4.8)	36 (45.0)	513 (49.4)	552 (47.0)	2 (66.7)	21 (56.8)	238 (67.6)	261 (66.6)
Moderate effect	659 (42.1)	2 (4.8)	30 (37.5)	433 (41.7)	465 (39.6)	1 (33.3)	14 (37.8)	179 (50.9)	194 (49.5)
Major effect	145 (9.3)	0 (0.0)	6 (7.5)	78 (7.5)	85 (7.2)	1 (33.3)	7 (18.9)	52 (14.8)	60 (15.3)
Death	9 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	7 (2.0)	7 (1.8)
Not followed (at most minimal clinical effects possible)	139 (8.9)	12 (28.6)	7 (8.8)	101 (9.7)	124 (10.6)	0 (0.0)	2 (5.4)	13 (3.7)	15 (3.8)
Unable to follow (potentially toxic exposure)	152 (9.7)	7 (16.7)	7 (8.8)	108 (10.4)	124 (10.6)	0 (0.0)	3 (8.1)	25 (7.1)	28 (7.1)
Total[a]	1566	42	80	1039	1174	3	37	352	392

HCF: health care facility; PCC: poison control center
[a]Study total and subtotals include exposures with an unknown age.
[b]Column percentages may not sum to 100.0% because of rounding error.

HCF. Most of the exposed individuals were already in or en route to a HCF when the PCC was called (79.2%) or were referred by a PCC to a HCF (9.8%) (Table 2). Overall, 44.4% of exposures were treated and released, and 31.8% were admitted to a HCF. More than half (51.9%) of the exposures resulted in a serious medical outcome (including 9.3% with major effects) and 23.8% resulted in minor effects. Compared with single-substance exposures, multiple-substance exposures were associated with greater odds of HCF admission (OR: 2.80; 95% CI: 2.21–3.55) and serious medical outcome (OR: 2.25; 95% CI: 1.77–2.85).

Among the 1174 single-substance exposures, the percentage resulting in HCF admission or a serious medical outcome was higher among adolescents and adults compared with children ≤12 years (Table 2). The odds of being admitted to a HCF (OR: 0.73, 95% CI: 0.42–1.27) or experiencing a serious medical outcome (OR: 0.84, 95% CI: 0.53–1.32) were similar for adolescents compared with adults.

Table 3. Selected clinical effects associated with single-substance kratom exposures by age group, NPDS 2011–2017.

Selected clinical effects	Total *n* (%[a])	≤12 years *n* (%[a])	13–19 years *n* (%[a])	≥20 years *n* (%[a])	Unknown *n* (%[a])
Single-substance exposure total	1174	42	80	1039	13
Neurological					
Agitated/irritable	269 (22.9)	4 (9.5)	13 (16.3)	248 (23.9)	4 (30.8)
Drowsiness/lethargy	168 (14.3)	4 (9.5)	15 (18.8)	149 (14.3)	0 (0.0)
Confusion	125 (10.6)	1 (2.4)	11 (13.8)	113 (10.9)	0 (0.0)
Seizures (single/multiple)	113 (9.6)	0 (0.0)	9 (11.3)	103 (9.9)	1 (7.7)
Tremor	79 (6.7)	0 (0.0)	3 (3.8)	76 (7.3)	0 (0.0)
Dizziness/vertigo	62 (5.3)	0 (0.0)	5 (6.3)	56 (5.4)	1 (7.7)
Hallucinations/delusions	61 (5.2)	0 (0.0)	4 (5.0)	57 (5.5)	0 (0.0)
Coma	37 (3.2)	0 (0.0)	2 (2.5)	35 (3.4)	0 (0.0)
Ataxia	29 (2.5)	0 (0.0)	3 (3.8)	26 (2.5)	0 (0.0)
Headache	27 (2.3)	0 (0.0)	1 (1.3)	26 (2.5)	0 (0.0)
Syncope	23 (2.0)	0 (0.0)	6 (7.5)	17 (1.6)	0 (0.0)
Slurred speech	19 (1.6)	0 (0.0)	2 (2.5)	17 (1.6)	0 (0.0)
Muscle weakness	12 (1.0)	0 (0.0)	1 (1.3)	11 (1.1)	0 (0.0)
Cardiovascular					
Tachycardia	251 (21.4)	1 (2.4)	16 (20.0)	234 (22.5)	0 (0.0)
Hypertension	119 (10.1)	0 (0.0)	7 (8.8)	112 (10.8)	0 (0.0)
Conduction disturbance	33 (2.8)	0 (0.0)	1 (1.3)	32 (3.1)	0 (0.0)
Chest pain (including non-cardiac)	31 (2.6)	0 (0.0)	1 (1.3)	30 (2.9)	0 (0.0)
Hypotension	21 (1.8)	0 (0.0)	0 (0.0)	21 (2.0)	0 (0.0)
Bradycardia	14 (1.2)	0 (0.0)	0 (0.0)	14 (1.3)	0 (0.0)
Cardiac arrest/asystole	5 (0.4)	0 (0.0)	0 (0.0)	5 (0.5)	0 (0.0)
Gastrointestinal					
Nausea	171 (14.6)	0 (0.0)	15 (18.8)	153 (14.7)	3 (23.1)
Vomiting	155 (13.2)	4 (9.5)	16 (20.0)	134 (12.9)	1 (7.7)
Abdominal pain	76 (6.5)	0 (0.0)	5 (6.3)	71 (6.8)	0 (0.0)
Diarrhea	33 (2.8)	1 (2.4)	1 (1.3)	31 (3.0)	0 (0.0)
Respiratory					
Respiratory depression	42 (3.6)	0 (0.0)	1 (1.3)	41 (3.9)	0 (0.0)
Dyspnea	28 (2.4)	0 (0.0)	3 (3.8)	24 (2.3)	1 (7.7)
Hyperventilation/tachypnea	21 (1.8)	1 (2.4)	1 (1.3)	19 (1.8)	0 (0.0)
Respiratory arrest	6 (0.5)	0 (0.0)	0 (0.0)	6 (0.6)	0 (0.0)
Cyanosis	4 (0.3)	0 (0.0)	1 (1.3)	3 (0.3)	0 (0.0)
Hematologic/hepatic					
AST, ALT > 100	59 (5.0)	0 (0.0)	2 (2.5)	57 (5.5)	0 (0.0)
Bilirubin increased	30 (2.6)	0 (0.0)	1 (1.3)	29 (2.8)	0 (0.0)
Other LFT abnormality	18 (1.5)	0 (0.0)	0 (0.0)	18 (1.7)	0 (0.0)
Renal					
Creatinine increased	11 (0.9)	0 (0.0)	0 (0.0)	11 (1.1)	0 (0.0)
Renal failure	6 (0.5)	0 (0.0)	0 (0.0)	6 (0.6)	0 (0.0)
Miscellaneous					
Diaphoresis	47 (4.0)	0 (0.0)	1 (1.3)	46 (4.4)	0 (0.0)
Electrolyte abnormality	34 (2.9)	0 (0.0)	2 (2.5)	32 (3.1)	0 (0.0)
Fever/hyperthermia	27 (2.3)	0 (0.0)	1 (1.3)	26 (2.5)	0 (0.0)
Rhabdomyolysis	10 (0.9)	0 (0.0)	0 (0.0)	10 (1.0)	0 (0.0)

[a]Column percentages for selected clinical effects were calculated by using the study's total number of single-substance exposures as the denominator and may sum to >100.0% because some exposures resulted in >1 clinical effect.

Clinical effects and therapies

Of the 1174 single-substance kratom exposures, 86.9% resulted in one or more clinical effects. The most common clinical effects were agitation/irritability (22.9%), tachycardia (21.4%), nausea (14.6%), drowsiness/lethargy (14.3%), vomiting (13.2%), confusion (10.6%), and hypertension (10.1%) (Table 3). Serious clinical effects included seizures ($n = 113$), respiratory depression ($n = 42$), coma ($n = 37$), increased bilirubin ($n = 30$), bradycardia ($n = 14$), rhabdomyolysis ($n = 10$), renal failure ($n = 6$), respiratory arrest ($n = 6$), cardiac arrest/asystole ($n = 5$), and cyanosis ($n = 4$). Among the individuals who experienced at least one clinical effect, 33.6% of effects lasted ≤8 h, 52.9% ≤24 h, and 13.7% >24 h.

More than half (51.9%) of individuals with a single-substance kratom exposure received one or more therapies. The most common therapies received were IV fluids (52.0%), benzodiazepines (31.3%), oxygen (14.7%), and naloxone (12.5%) (Table 4). An additional 8.6% of exposures resulted in tracheal intubation.

Children ≤ 12 years

Among the 48 kratom exposures that involved children ≤12 years, 68.8% were children <2 years, including seven neonates. One exposure was identified as having occurred *via* breast-feeding. Most were unintentional (81.3%) and single-substance exposures (87.5%) (Table 1). Of the 42 single-substance exposures in this age group, 14.3% resulted in HCF admission and 4.8% experienced a serious medical outcome (Table 2).

All seven neonatal exposures occurred during 2016–2017; of which, five were single-substance kratom exposures, one

Table 4. Selected therapy received by individuals with single-substance kratom exposures, NPDS 2011–2017.

Selected therapy	*n* (%[a])
Single substance exposure total	1174
Fluids, IV	610 (52.0)
Benzodiazepines	368 (31.3)
Other	260 (22.1)
Oxygen	173 (14.7)
Naloxone	147 (12.5)
Sedation (other)	140 (11.9)
Intubation	101 (8.6)
Antiemetics	89 (7.6)
Dilute/irrigate/wash	68 (5.8)
Vasopressors	17 (1.4)
CPR	12 (1.0)
Antihypertensives	11 (0.9)
Anticonvulsants	10 (0.9)
Antiarrhythmic	8 (0.7)
Hemodialysis	5 (0.4)

[a]Column percentages for selected therapies were calculated by using the study's total number of single-substance exposures as the denominator and sum to >100.0% because some exposures received >1 therapy.

involved first-ranked kratom, and one involved first-ranked tramadol. Among the six neonates with a single-substance or first-ranked kratom exposure, three were admitted to a CCU, two were admitted to a non-CCU, one experienced a major effect, one experienced a moderate effect, and two were unable to be followed, but judged as potentially toxic exposures. Among five neonates experiencing withdrawal, four were exposed to kratom alone and one was exposed to kratom (first-ranked) and kava kava. Three of the five neonates exposed to single-substance kratom experienced one or more clinical effects, including agitation/irritability ($n = 2$), diarrhea ($n = 1$), and hyperventilation/tachypnea ($n = 1$). Agitation/irritability, electrolyte abnormality, elevated (>100) AST or ALT levels, hypoglycemia, fasciculations, and dyspnea were also observed for a neonate exposed to kratom (first-ranked) and kava kava.

Adolescents (13–19 years)

Of the 137 adolescent exposures, 41.6% were multiple-substance exposures and 84.7% were among 17–19 year-olds. Most exposures among adolescents were intentional abuse or misuse (75.9%) or suspected suicide (10.2%) (Table 1). Of the 117 first-ranked kratom exposures, 43.6% were treated and released, 33.3% were admitted to a HCF, and 48.7% experienced serious medical outcomes with no fatalities. Among the 80 adolescents with a single-substance kratom exposure, 90.0% experienced one or more clinical effects (Table 3).

Adults (>20 years)

Adults 20–39 years old accounted for 73.6% of kratom exposures among the adult age group. The majority of kratom exposures among adults were single-substance (64.7%) and occurred among males (70.7%) (Table 1). Intentional abuse or misuse (59.9%) was the most common reason of exposure, followed by suspected suicide (9.3%) and adverse reaction (8.4%). Of the 1391 first-ranked kratom exposures, 45.7% were treated/evaluated and released, 32.4% resulted in HCF admission, and 54.0% resulted in a serious medical outcome.

There were 11 deaths associated with kratom exposures and all were among adults ages 22–38 years. Two deaths involved single-substance kratom exposures and nine deaths involved multiple-substance exposures. Kratom was the first-ranked substance in seven of the multiple-substance deaths, and "acetaminophen with diphenhydramine" and "other or unknown narcotics" were the first-ranked substances for the remaining two deaths. Co-substances involved in the deaths included diphenhydramine, ethanol beverages, benzodiazepines, caffeine, fentanyl, and cocaine. The AAPCC fatality review committee reviewed four of the nine deaths in which kratom was the only or first-ranked substance involved and determined that kratom was "probably responsible" in three deaths and "unknown" if responsible in one death.

Discussion

This study provides an in-depth analysis of national data on kratom exposures. The only previous national analysis of kratom exposures was a brief report and included exposures through 2015 [3]. Because two-thirds of the exposures in this study occurred in 2016–2017, it provides important new information about the characteristics and trends of kratom exposures in the US. During the 7-year study period, 1807 kratom exposures were reported to PCCs across the US, and exposure frequency increased 52-fold. This observed increase was mainly attributable to a >40-fold increase among adults ≥20 years and adolescents, who accounted for most of the exposures in this study. This increase was most likely driven by the increase in kratom use nationally [1,3,10,16,17]. According to surveys of kratom users, the majority of kratom users are adults 31–50 years and many use kratom for treatment of chronic or acute pain and mood conditions, such as depression and anxiety. Others report using kratom to decrease or abstain from use of non-prescription opioids, including heroin, or as a substitute for these substances [7–9,15]. This study found that kratom exposure rates were highest in Idaho and Oregon and lowest in Delaware and Wisconsin, varying from 3.9 to 0.2 exposures per million state residents. It is unclear whether this variation reflects different kratom use rates, reporting rates to PCCs, or other factors.

There were seven neonatal exposures reported during the study period and five were attributed to kratom withdrawal. There has been one report of neonatal kratom dependence in Canada and one suspected case of neonatal kratom withdrawal in Thailand [18,19]. Clinical effects observed for single-substance kratom exposures among the neonates included agitation/irritability, diarrhea, and hyperventilation/tachypnea. These neonatal withdrawal cases suggest that transplacental transfer is possible and that healthcare providers should educate pregnant women on the risks of kratom use during pregnancy. Notably, although not in a neonate, one exposure was documented as having occurred through breast milk. Thus, the possibility of exposure via breast milk should also be communicated to new mothers who use kratom.

The clinical effects observed in this study highlight that despite its classification as an herbal supplement, kratom can have serious physiologic effects. Kratom leaves contain more than 25 alkaloids, but it is believed that the primary active alkaloids are mitragynine and 7-hydroxymitragynine (7-HMG). Both mitragynine and 7-HMG are selective, full agonists of μ-opioid receptors, while mitragynine also blocks serotonergic-$5HT_{2A}$ receptors and stimulates postsynaptic alpha-2 adrenergic receptors [10]. Prozialeck noted that despite studies showing interaction of these compounds with opioid receptors, the effects of kratom are not typical of other opioid agonists [1]. Common non-opioid effects noted in our study included tachycardia, agitation/irritability, seizures, and hypertension. The nociceptive properties of kratom are partially due to norepinephrine and serotonin effects and are not fully reversed by opiate antagonists [20]. This dual pathway nociceptive effect and the mixed clinical presentation in overdose is similar to tramadol and tapentadol. There have been previous case reports of intrahepatic cholestasis, seizures, and coma following kratom exposure, supporting the concern for other non-opioid effects [12,13,21]. The clinical effects reported in this study, including seizures (113 cases), coma (37 cases), increased bilirubin (21 cases), and renal failure (6 cases), provide additional evidence of kratom toxicities.

In this study, more than one-third of exposures resulted in HCF admission and more than half of exposures resulted in a serious medical outcome, especially among adolescents and adults. These high percentages reflect the potential toxicity of the active compounds found in kratom leaves [11,12,21]. One study found that kratom extracts inhibit multiple CYP450 enzymes *in vitro*, which could result in interactions with other prescription and over-the-counter drugs [10]. This may contribute to the finding that kratom exposures involving multiple substances have higher odds of HCF admission and a serious medical outcome compared with single-substance kratom exposures. In addition, 9 of the 11 deaths reported in this study involved kratom plus other substances, such as diphenhydramine, ethanol beverages, caffeine, benzodiazepines, fentanyl, and cocaine. Other deaths involving kratom have been previously reported [10,22].

The high proportions of HCF admissions and serious medical outcomes highlight the need for kratom regulation by the FDA to ensure quality and safety, as well as the need for more research on the effects of kratom in humans. Currently, kratom is considered a dietary supplement, and therefore, is not subject to the same FDA safety regulations as other drugs [23]. Although there is no federal ban on kratom, a number of states, the District of Columbia, and smaller jurisdictions have banned its use [24]. Kratom is easily purchased online without adequate safeguards for product purity [25]. For example, in Sweden, it was found that one kratom-containing product available online, Krypton, also contained the active metabolite of tramadol, O-desmethyltramadol, which was believed to have contributed to nine deaths [26]. Additionally, Lydecker et al. analyzed multiple commercial kratom products for mitragynine and 7-HMG, and found that many contained substantially higher concentrations of 7-HMG than found in natural kratom leaves, with an increase of up to 500%, suggesting artificial addition of 7-HMG to these products [27]. Lastly, Salmonella contamination of kratom products has occurred, resulting in a recall by the FDA [28].

Study limitations

This study has several limitations. Not all adverse events associated with kratom exposure are reported to PCCs; therefore, this study underestimates the true number of these exposures. Reported exposures do not necessarily represent a poisoning or overdose, and repeat exposures cannot be identified since no individual identifiers are collected by the NPDS. The NPDS categorization for reason for exposure does not yield information on the motivation for exposure, so exposures coded as "intentional" do not differentiate between use for recreational purposes and pain relief. Clinical effects of kratom exposure in humans are not well defined, so clinical effects were included in this study if they were classified as "related" or "unknown if related" to exposure. NPDS data are self-reported and cannot be fully verified by the PCCs or AAPCC, but NPDS data are entered by highly qualified poison experts using strict quality controls and case follow-up methods.

Conclusions

As the opioid crisis continues in the US, kratom use has increased as an alternative method for the self-management of pain and opioid withdrawal. Despite the perception that kratom is safe because it is classified as an herbal supplement, a variety of serious medical outcomes following exposure to kratom have been documented, especially when kratom is used in combination with other substances. More research is needed to define the human response to kratom. At a minimum, kratom products should be free of potentially harmful contaminants, provide a uniform strength of active ingredients, and have appropriate labeling. Increased regulation of kratom products would help guarantee product quality and safety. Individuals who choose to use kratom should be educated about its potential risks, including the dangers of using it in combination with other substances.

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Geolocation information

The study area includes the 50 states and District of Columbia, United States of America.

Disclosure statement

No potential conflict of interest was reported by the authors.

Data availability statement

Data for this study were provided by the American Association of Poison Control Centers from its proprietary database, the National Poison Data System.

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