Ashdin Publishing
Journal of Drug and Alcohol Research
Vol. 11 (2022), Article ID 236162, 10 pages
doi:10.4303/jdar/236162

Research Article

Clinical Characteristics of Kratom Exposures Reported to the Georgia and Alabama Poison Control Centers from 2016–2020: A Retrospective Review

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Received: 31 January, 2022; Manuscript No: jdar-22-52870; **Editor assigned:** 02 February, 2022; PreQC No: jdar-22-52870 (PQ); **Reviewed:** 16 February, 2022; QC No: jdar-22-52870; **Revised:** 21 February, 2022; Manuscript No: jdar-22-52870(R); **Published:** 28 February2022; **DOI:**10.4303/jdar/236162

Abstract

Kratom is a plant that is indigenous to Southeast Asia and has recently attracted attention in the United States; its primary active alkaloid mitragynine has stimulant effects at low doses and sedative effects at high doses. The purpose of this study was to provide updated information on the characteristics, clinical effects, treatment and patient outcomes of kratom exposure.

Methods: This was a retrospective analysis of kratom exposures reported to two statewide poison control centers between January 2016 and June 2020. Subjects who reported coexposure to other substances of abuse or intentional xenobiotic overdoses were excluded. The data were stratified by the consumption of kratom alone and with nonoverdose exposure to other medications.

Results: In total, 153 kratom exposures were included. Patients were classified into 3 groups according to kratom use within the past 24 hours: low dose (1–5 g; 45.1%), moderate dose (>5–15 g; 17.0%) and high dose (>15 g; 12.4%) groups.

The two common clinical effects were central nervous system excitation (kratom, 32.3%; coexposure, 53.3%) and tachycardia (kratom, 46.6%; coexposure, 44.6%). Dose dependent sedative effects of kratom were not observed. Coexposure accounted for 39.2% of cases and was associated with higher rates of ICU admission (28.3% vs. 8.6%; $p<0.01$) and serious medical outcomes (28.3% vs. 7.5%; $p<0.01$).

Conclusion: Kratom exposure is associated with a wide range of symptoms. Despite the perception that kratom is safe, the probability of more severe symptoms and serious effects should be of concern, particularly when kratom is used with other medications.

Keywords: Kratom; Mitragyna speciosa; Mitragynine; 7-Hydroxymitragynine; Poison Control center; National poison data system; Dietary supplement

Introduction

Kratom, or Mitragyna speciosa, has been consumed for hundreds of years in Southeast Asia by chewing the raw leaves of the plant or brewing them in the form of tea. Kratom has gained increasing attention in the United States, resulting in its increased use. The main active alkaloid substances in kratom are mitragynine and 7-hydroxymitragynine (7-HMG), which affect the central nervous system (CNS) and have mild stimulant effects at low doses (1–5 g) and opioid like and sedative effects at moderate (>5–15 g) to high doses (>15 g) [1]. Kratom use in the United States began as a possible alternative to opioid therapy; however, the slight mind altering effects of kratom have recently led to its recreational use, misuse, and overuse [2].

With increasing kratom use among adults and adolescents, the number of kratom exposures reported to US poison control centers (PCCs) increased by more than 40 fold from 2011 to 2017 [3]. Two recent studies in the US showed a 0.8% prevalence of kratom use in adults aged ≥18 years [4] in 2018 and a 0.7% prevalence in individuals aged ≥12 years in 2019 [5]. Additionally, an increase was found in the number of reported adverse effects associated with kratom, prompting the Drug Enforcement Administration (DEA) to consider listing kratom as a Schedule I drug, and it has never been approved for medical use [6,7].

Although several studies have been conducted to elucidate the pharmacological properties of kratom, additional studies are warranted to investigate the human body's response to kratom. To date, studies published in the literature have revealed the role of mitragynine in altering consciousness and causing seizures, lethargy, intrahepatic cholestasis, and tachycardia [8-10]. A 2011–2017 review from the National Poison Data System (NPDS) also reported myocardial infarction, arrhythmias, and hypertension following the administration of kratom, particularly when used with oth-

er substances [3]. A recent review reported that most kratom related deaths were associated with polysubstance use (CNS depressants, opioids, benzodiazepines and alcohol), with 95% of deaths occurring in patients with a current drug abuse history and various underlying health issues [11].

The goal of this study was to provide information on the characteristics of kratom use, including the clinical effects, treatments and patient outcomes. The secondary aim was to delineate the characteristics of single substance kratom exposure compared with the clinical effects when kratom is coexposed. This study provides updated information on the characteristics of kratom use reported to two statewide PCCs, which may help guide healthcare and public health professionals as kratom use increases worldwide.

Methods

Data sources and study design

This was a retrospective study of human kratom exposure reported to two PCCs over a 4 year period from January 1, 2016, to June 30, 2020. The two centers were the Georgia Poison Center (GPC) and the Alabama Poison Information Center (APIC), which cover a population of approximately 14 million people. The present study was approved by the Institutional Review Boards of Emory University and the University of Alabama at Birmingham.

Electronic health records were queried from the Tox Sentry system, which is an electronic medical record system designed by the GPC in partnership with the Florida Poison Center that is currently used by 8 PCCs in the United States. Kratom exposure in patients of all ages was identified using the product codes of the American Association of Poison Control Centers (AAPCC) for "Plants-Mitragyna" and "Mitragyna speciosa Korthals" (botanical name), along with the generic code for "Kratom" in cases with a missing product code. Subjects exposed to other pharmaceuticals at therapeutic doses were included. The exclusion criteria were no kratom exposure (e.g., informational calls) and miscoded kratom exposures (e.g., coded as tianeptine). Subjects were also excluded if they used nonkratom substances of abuse (including ethanol, illicit drugs, and cannabis products) or had a history of other xenobiotic overdoses. All data were reviewed and recorded in electronic spreadsheets by three trained data abstractors using the data abstraction form. Any discrepancies in coding were reviewed jointly and discussed to clarify any issues.

Variables

The subjects were divided into three age groups: children (<12 years), adolescents (12–18 years), and adults (>18 years). Because different kratom doses can affect clinical manifestations, the subjects were stratified into 3 groups according to the self-reported dose of kratom exposure within the past 24 hours: the low dose group (1–5 g); the moderate dose group (>5–15 g); and the high dose group (>15 g) [1,3]. In acute exposure patients, the dose was calculated from the patient's report of the total dose the patient took during acute exposure. The reasons for using kratom were classified as unintentional, intentional and unknown. Intentional use was subdivided into attempted suicide, abuse or misuse, therapeutic (used for therapeutic intent) and unknown. Kratom products were classified as powder (including tablets and capsules), tincture (a liquid form of kratom extract) and botanical (chewing leaves, brewing tea from leaves). When the form of the product was not evident, it was classified as "unknown."

Other factors analyzed herein were the method of exposure, clinical effects, treatments, level of care received and medical outcomes, which were classified according to the AAPCC [12]. A "minor outcome" was defined as limited symptoms or symptoms that did not require treatment and resolved rapidly with no residual disability (e.g., self-limited gastrointestinal symptoms, drowsiness, or sinus tachycardia without hypotension). A "moderate outcome" was defined as more pronounced or prolonged symptoms or symptoms that generally required treatment but were not life threatening and did not cause permanent disability (e.g., disorientation, agitation, hypotension that was rapidly responsive to treatment or isolated seizures that responded readily to treatment). A "major outcome" was defined as life threatening symptoms or symptoms that caused a permanent loss of function (e.g., repeated seizures or status epilepticus, rhabdomyolysis, or cardiorespiratory compromise requiring intubation). Heart rate, blood pressure and electrocardiogram (EKG) values were collected from the initial presenting data, but some EKG data may have been obtained later in the course of treatment at the healthcare facility. Subanalyses were performed to identify differences in clinical symptoms and outcomes between subjects exposed only to kratom and those coexposed to therapeutic dose pharmaceuticals.

Statistical analysis

The data were described using descriptive statistics. SPSS version 24 (IBM Corp., Armonk, NY, USA) was used to conduct the data analysis. Pearson's chi-squared tests with 95% confidence intervals (CIs) were used to test for the associations of dichotomous outcomes, and Fisher's exact test was used when the frequency of events was low (<5 in any data field). Our investigation adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Results

In total, 219 cases of kratom exposure reported to the Georgia and Alabama PCCs from January 2016 to June 2020 were identified. After applying the exclusion criteria, 153 (69.8%) cases were included in the data analysis. Among these, 60.8% (n=93) were single substance exposures (Figure 1). Based on age, the subjects were categorized as children <12 years (n=7, 4.6%), adolescents 12–18 years (n=4, 2.6%), or adults >18 years (n=139, 90.8%) (Table 1). Males constituted a majority of the subjects (n=110, 71.9%).

Most of the consultations originated from a health care facility (n=134, 87.6%), involved acute exposures (n=103, 67.3%), and reported symptoms (n=144, 94.1%). The es-

timated product dose was reported in 93.5% of exposures. Powdered kratom, including concentrated forms (tablets and capsules), accounted for most of the exposures across all age groups (n=124, 81.0%). Exposures to the liquid form of kratom extract, known as a tincture, and botanical products, such as kratom tea and fresh leaves, were less frequently reported (n=16 [10.5%] and n=3 [2.0%], respectively). Exposure via ingestion was reported more frequently than exposure via other routes across all age groups (**Table 1**).

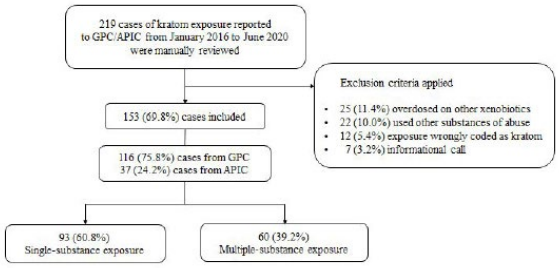

Figure 1: Inclusion and exclusion flow chart with reasons for exclusion.

Table 1: Details and clinical effects of kratom exposure by age

	Children (<12 years) (n=7, 4.6%)	Adolescents (12–18 years) (n=4, 2.6%)	Adults (>18 years) (n=139, 90.8%)	Total (n=153)
Type of exposure				
Single substance	7 (100%)	3 (75%)	80 (58.0%)	93 (60.8%)
Multiple substances	0	1 (25%)	59 (42.8%)	60 (39.2%)
Sex				
Male	5 (71.4%)	3 (75%)	101 (72.7%)	110 (71.9%)
Female	2 (28.6%)	1 (25%)	38 (27.3%)	43 (28.1%)
Chronicity				
Acute	7 (100.0%)	4 (100.0%)	91 (65.5%)	103 (67.3%)
Chronic	0	0	29 (20.9%)	30 (19.6%)
Acute-on-chronic	0	0	19 (13.7%)	20 (13.1%)
Symptom status				
Symptomatic	**2 (28.6%)**	4 (100.0%)	135 (97.1%)	144 (94.1%)
Asymptomatic	5 (71.4%)	0	4 (2.9%)	9 (5.9%)
Caller				
ED or hospital floor	2 (28.6%)	4 (100.0%)	127 (91.4%)	134 (87.6%)
Home	5 (71.4%)	0	12 (8.6%)	19 (12.4%)
Dose (past 24 hours)				
Low (1–5 g)	7 (100.0%)	3 (75%)	57 (41.0%)	69 (45.1%)
Moderate (>5–15 g)	0	1 (25%)	24 (17.3%)	26 (17.0%)
High (>15 g)	0	0	19 (13.7%)	19 (12.4%)
Unknown	0	0	39 (28.1%)	39 (25.5%)
Product type				
Capsule, tablets	7 (100.0%)	4 (100.0%)	111 (79.9%)	124 (81.0%)
Concentrated	0	0	16 (11.5%)	16 (10.5%)
Botanical	0	0	2 (1.4%)	3 (2.0%)
Unknown	0	0	10 (7.2%)	10 (6.5%)
Exposure route				
Ingestion	7 (100.0%)	4 (100.0%)	129 (92.8%)	143 (93.5%)
Nasal insufflation	0	0	9 (6.5%)	9 (5.9%)
Intent of exposure				
Intentional	0	4 (100.0%)	133 (95.7%)	140 (91.5%)
• Abuse/misuse	0	2 (50.0%)	87 (62.6%)	90 (58.8%)
• Suspected suicide	0	1 (25.0%)	25 (18.0%)	26 (17.0%)
• Therapeutic	0	0	18 (12.9%)	20 (13.1%)
• Withdrawal	0	0	3 (2.2%)	3 (2.0%)
• Unknown	0	1 (25.0%)	0	1 (0.7%)
Unintentional	7 (100.0%)	0	5 (3.6%)	12 (7.8%)
Unknown	0	0	1 (0.7%)	1 (0.7%)

All exposures in children were accidental, while most of the adolescent and adult exposures were intentional. There were 133 intentional exposures in adults (95.7%). The intent of these exposures was abuse (n=87, 62.6%), attempted suicide (n=25, 18.0%), therapy (n=18, 12.9%), or alleviation of reported withdrawal symptoms (n=3, 2.2%) (Table 1). All unintentional exposures (n=12, 7.8%) involved people exposed to low doses of kratom, and most of these cases (n=7, 58.3%) were managed at home.

Clinical effects of kratom exposure

Kratom dosing information was available in 114 cases (74.5%). Clinical effects were reported in 144 (94.1%) subjects. A total of 90.4% of subjects who used only kratom reported symptoms, which was lower than the 98.3% who coexposed the substance with other prescribed medi-

cations (Table 2). The two most common clinical effects were CNS excitation (kratom only, 32.3%; coexposure, 53.3%) and tachycardia (kratom only, 46.6%; coexposure, 44.6%). High dose kratom did not result in a difference in CNS excitation effects compared to low dose kratom only exposure (41.7% vs. 25.6%; 95% CI: 0.6–4.1 in the high dose group compared to the low dose group regarding CNS excitation). Coexposure was associated with a higher incidence of any neurological symptoms, with a relative risk (RR) of 1.40 (95.0% vs. 67.7%; 95% CI: 1.2–1.6; p<0.01). Among the reported gastrointestinal (GI) symptoms, nausea with (n=15, 9.8%) or without vomiting (n=17, 11.1%) was reported more frequently than other GI symptoms. Four subjects (2.6%) had increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels >100 U/L, and two subjects (1.3%) had increases in bilirubin levels (**Table 2**).

Table 2: Detailed clinical effects following kratom exposure by dose and coexposure

	Low dose (1–5 g) (n=69, 45.1%)		**Moderate dose (>5–15 g) (n=26, 17.0%) n**		**High dose (>15 g) (n=19, 12.4%)**		**Total (n=153)**	
	Single (n=43	**Coexposure (n=26)**	**Single (n=17)**	**Coexposure (n=9)**	**Single (n=12)**	**Coexposure (n=7)**	**Single (n=93)**	**Coexposure (n=60)**
Symptomatic	38 (88.4%)	25 (96.2%)	15 (88.2%)	9 (100%)	11 (91.7%)	7 (100%)	85 (90.4%)	59 (98.3%)
Neurologic (any)	24 (55.8%)	24 (92.3%)**	14 (82.4%)	9 (100%)	9 (75.0%)	7 (100%)	63 (67.7%)	57 (95.0%)**
CNS excitation	11 (25.6%)	14 (53.8%)*	9 (52.9%)	5 (55.6%)	5 (41.7%)	3 (42.9%)	30 (32.3%)	32 (53.3%)**
Anxiety, paranoia	4 (9.3%)	10 (38.5%)	1 (5.9%)	2 (22.2%)	4 (33.3%)	1 (14.3%)	10 (10.8%)	16 (26.7%)
Hallucinations, psychosis	2 (4.7%)	2 (7.7%)	1 (5.9%)	1 (11.1%)	1 (8.3%)	0	6 (6.5%)	5 (8.3%)
Agitated, aggressive	4 (9.3%)	4 (9.3%)	5 (29.4%)	3 (33.3%)	1 (8.3%)	0	11 (11.8%)	12 (21.7%)
Seizure	1 (2.3%)	0	3 (17.6%)	1 (11.1%)	0	1 (14.3%)	5 (5.4%)	4 (6.7%)
Tremors, myoclonus	2 (4.7%)	1 (3.8%)	4 (23.5%)	0	0	1 (14.3%)	7 (7.5%)	5 (8.3%)
CNS depression	6 (14.0%)	8 (30.8%)	3 (17.6%)	4 (44.4%)	2 (16.7%)	3 (42.9%)	20 (21.5%)	22 (36.7%)
Reduced consciousness	5 (11.6%)	6 (23.1%)	2 (11.8%)	1 (11.1%)	2 (16.7%)	1 (14.3%)	11 (11.8%)	9 (15.0%)
Comatose, unresponsive	1 (2.3%)	2 (7.7%)	1 (5.9%)	3 (33.3%)	0	2 (28.6%)	8 (8.6%)	12 (20.0%)
Confusion	3 (7.0%)	2 (7.7%)	1 (5.9%)	0	0	0	6 (6.5%)	3 (5.0%)
Speech abnormalities	0	0	0	0	0	0	2 (2.2%)	1 (1.7%)
Impaired coordination	0	1 (3.8%)	0	0	0	1 (14.3%)	0	2 (3.3%)
Other neurologic	7 (16.3%)	2 (7.7%)	2 (11.8%)	0	2 (16.7%)	1 (14.3%)	13 (14.0%)	3 (5.0%)
Altered (others)	2 (4.7%)	0	0	0	0	0	2 (2.2%)	0
Euphoria	1 (2.3%)	0	0	0	1 (8.3%)	0	2 (2.2%)	0
Unusual sensation	1 (2.3%)	2 (7.7%)	0	0	0	1 (14.3%)	2 (2.2%)	3 (5.0%)
Numbness, tingling	1 (2.3%)	0	1 (5.9%)	0	1 (8.3%)	0	5 (5.4%)	0
Headache	1 (2.3%)	0	0 (0%)	0	0	0	1 (1.1%)	0
Lightheaded, dizziness	3 (7.0%)	0	1 (5.9%)	0	0	0	4 (4.3%)	0
Gastrointestinal	16 (37.2%)	6 (23.1%)	3 (17.6%)	1 (11.1%)	3 (25.0%)	1 (14.3%)	29 (31.1%)	11 (18.6%)
Nausea only	10 (23.3%)	3 (11.5%)	0	0	1 (8.3%)	1 (14.3%)	13 (13.8%)	4 (6.8%)
Nausea and vomiting	6 (14.0%)	2 (7.7%)	2 (11.8%)	0	0	0	11 (11.7%)	4 (6.8%)
Abdominal pain, cramps	0	1 (3.8%)	1 (5.9%)	0	1 (8.3%)	0	2 (2.1%)	1 (1.7%)
Diarrhea	1 (2.3%)	0	0	0	1 (8.3%)	0	3 (3.2%)	0
AST, ALT > 100 U/L	0	0	0	1 (11.1%)	0	0	2 (2.1%)	2 (3.4%)

Palpitations	14 (32.6%)	11 (42.3%)	8 (47.1%)	2 (22.2%)	5 (41.7%)	3 (42.9%)	32 (34.4%)	21 (35.0%)
Heart rate	n=22	n=21	n=13	n=9	n=8	n=6	n=58	n=56
n Normal (60–100/min)	9 (40.9%)	12 (50.0%)	7 (53.8%)	4 (44.4%)	4 (50.0%)	3 (50.0%)	28 (48.3%)	31 (55.4%)
Bradycardia (< 60/min)	2 (9.1%)	0	0	0	0	0	3 (5.1%)	0
Tachycardia (> 100/min)	11 (50.0%)	12 (50.0%)	6 (46.2%)	5 (55.6%)	4 (50.0%)	3 (50.0%)	27 (46.6%)	25 (44.6%)
Blood pressure	n=22	n=24	n=13	n=9	n=8	n=6	n=58	n=56
Normal (90–140 mmHg)	9 (40.9%)	15 (62.5%)	8 (61.5%)	6 (66.7%)	6 (75.5%)	5 (83.3%)	35 (60.3%)	35 (62.5%)
SBP < 90 mmHg	1 (4.5%)	0	0	0	0	0	1 (1.7%)	0
SBP >140–180 mmHg	11 (50.0%)	9 (37.5%)	5 (38.5%)	3 (33.3%)	1 (12.5%)	1 (16.7%)	20 (34.5%)	18 (33.9%)
SBP > 180 mmHg	1 (4.5%)	0	0	0	1 (12.5%)	0	2 (3.4%)	2 (3.6%)
QTc interval	n=4	n=7	n=3	n=3	n=0	n=1	n=12	n=19
≤ 440	2 (50.0%)	5 (71.4%)	2 (66.7%)	2 (66.7%)	0	0	9 (75.0%)	9 (47.4%)
441–470	1 (25.0%)	2 (28.6%)	1 (33.3%)	1 (33.3%)	0	1 (100%)	2 (16.7%)	7 (36.8%)
> 470	1 (25.0%)	0	0	0	0	0	1 (8.3%)	3 (15.8%)

Vital signs and EKG data were reported in 114 (74.5%) and 31 (20.3%) cases, respectively; however, these analyses were limited (Table 2), as not all patients were evaluated at a healthcare facility. Among the subjects with heart rate data, tachycardia (heart rate >100/min) was the most frequent cardiovascular related manifestation following single and multiple substance exposures, but the proportions of subjects in each exposure group with a normal heart rate were nearly equivalent (48.3% vs. 55.4%, respectively). Among those with vital sign data in the kratom only group, those exposed to a low dose were more likely to have slightly elevated blood pressure (systolic blood pressure [SBP] >140–180 mmHg), while those in the other dosing groups were more likely to have normal blood pressure (SBP 90–140 mmHg). Although kratom only exposure did not affect the QTc interval, subjects who consumed kratom with other xenobiotics seemed to have a nonsignificant risk of QTc prolongation on their presenting EKGs (RR: 2.1 and 95% CI: 0.7–6.1 for QTc>440 msec; RR: 1.9 and 95% CI: 0.2–16.1 for QTc>470 msec) (Table 2). We identified torsade de pointes in one patient who used kratom in addition to her prescribed medications, namely, escitalopram and aripiprazole (Supplementary Table 1).

The proportion of patients in the multiple substance subgroup who received any treatment was higher than that in the single substance subgroup, with RRs of 1.75 (95% CI: 1.08–2.8; $p<0.05$) in the low dose group, 1.88 (95% CI: 1.08–3.2; $p<0.05$) in the moderate dose group, and 1.71 (95% CI: 0.6–4.8) in the high dose group. Benzodiazepines (n=33, 21.6%) were the most frequently administered therapy, followed by naloxone (n=21, 13.7%) and antiemetics (n=16, 10.5%) (**Table 3**).

Table 3: Detailed outcomes and therapies administered following kratom exposure by dose and coexposure

	Low dose (1–5 g) (n=69, 45.1%)		**Moderate dose (>5–15 g) (n=26, 17.0%)**		**High dose (>15 g) (n=19, 12.4%)**		**Total (n=153)**	
	Single (n=43)	**Coexposure (n=26)**	**Single (n=17)**	**Coexposure (n=9)**	**Single (n=12)**	**Coexposure (n=7)**	**Single (n=93)**	**Coexposure (n=60)**
Therapy (any, total)	16 (37.2%)	17 (65.4%)*	8 (47.1%)	8 (88.9%)*	4 (33.3%)	4 (57.1%)	36 (38.7%)	44 (71.6%)*
Benzodiazepines	6 (14.0%)	7 (26.9%)	5 (29.4%)	3 (33.3%)	2 (16.7%)	2 (28.6%)	16 (17.2%)	17 (28.3%)
Oxygen	1 (2.3%)	4 (15.4%)	1 (5.9%)	2 (22.2%)	1 (8.3%)	1 (14.3%)	6 (6.5%)	10 (16.7%)
Naloxone	1 (2.3%)	5 (19.2%)*	3 (17.6%)	2 (22.2%)	0	2 (28.6%)	8 (8.6%)	13 (21.7%)*
Sedation (other)	0	2 (7.7%)	1 (5.9%)	2 (22.2%)	0	0	4 (4.3%)	11 (18.3%)*
Intubation	1 (2.3%)	0	0	2 (22.2%)	0	1 (14.3%)	3 (3.2%)	8 (13.3%)
Antiemetic	5 (11.4%)	4 (15.4%)	2 (11.8%)	1 (11.1%)	1 (8.3%)	1 (14.3%)	9 (9.7%)	7 (11.7%)
Vasopressors	1 (2.3%)	0	0	0	0	0	1 (1.1%)	1 (1.7%)
CPR	1 (2.3%)	0	0	0	0	0	1 (1.1%)	0

Antiarrhythmic	0	0	0	0	0	0	0	1 (1.7%)
Hemodialysis	1 (2.3%)	0	0	0	0	0	0	1 (1.7%)
Others	2 (4.5%)	1 (4.7%)	0	3 (33.3%)	0	0	2 (2.1%)	5 (8.3%)
Disposition								
Home (no HCF)	9 (20.9%)	0	1 (5.9%)	0	2 (16.7%)	1 (14.3%)	13 (14.0%)	1 (1.7%)*
Released from ED	28 (65.1%)	17 (65.4%)	11 (64.7%)	3 (33.3%)	5 (41.7%)	2 (28.6%)	53 (57.0%)	29 (48.3%)
Ward admission	2 (4.7%)	7 (26.9%)	3 (17.6%)	1 (11.1%)	1 (8.3%)	1 (14.3%)	9 (9.7%)	10 (16.7%)
ICU admission	2 (4.7%)	2 (7.7%)	1 (5.9%)	5 (55.6%)	1 (8.3%)	2 (28.6%)	8 (8.6%)	17 (28.3%)**
Lost follow up/AMA	2 (4.7%)	0	1 (5.9%)	0	2 (16.7%)	1 (14.3%)	10 (10.8%)	3 (5.0%)
Medical outcome								
No effect	8 (18.6%)	1 (3.8%)	2 (11.8%)	0	1 (8.3%)	0	13 (14.0%)	1 (1.7%)*
Minor effect	24 (55.8%)	13 (50.0%)	5 (29.4%)	1 (11.1%)	6 (50.0%)	3 (42.9%)	42 (45.2%)	18 (30.0%)
Moderate effect	7 (16.3%)	10 (38.5%)	8 (47.1%)	4 (44.4%)	2 (16.7%)	0	21 (22.6%)	21 (35.0%)
Major effect	2 (4.7%)	2 (7.7%)	1 (5.9%)	4 (44.4%)	0	3 (42.9%)	7 (7.5%)	17 (28.3%)**
Death	0	0	0	0	0	0	1 (1.1%)	0
Unable to follow	2 (4.7%)	0	1 (5.9%)	0	3 (25.0%)	1 (14.3%)	9 (9.7%)	3 (5.0%)

Clinical outcomes of kratom exposure

In this study, most patients with kratom exposure visited the emergency department (52.7%), with 12.4% of subjects admitted to a hospital floor and 16.3% admitted to an ICU. There were more subjects with minor clinical effects (n=60, 39.2%) than with moderate (n=34, 22.2%) or major clinical effects (n=24, 15.7%). Among the 72 (47.0%) single exposures with a known kratom dosage (Table 3), subjects who were exposed to a low dose of kratom were generally discharged from the emergency department (n=28, 65.1%). In subjects exposed only to kratom, no difference in intensive level care was observed in the moderate dose group (5.9% vs. 4.7%; RR: 1.26; 95% CI: 0.1–13.0) or high dose group (8.3% vs. 4.7%; RR: 1.79; 95% CI: 0.2–18.1) compared to the low dose group.

Major effects were more likely following nonoverdose pharmaceutical drug coexposure. A total of 24 subjects (15.7%) experienced major effects related to kratom, in which coexposures caused more serious medical outcomes than kratom only exposures (28.3% vs. 7.5%; 95% CI: 1.7 to 8.5, $p<0.01$) (Table 3). The rates of major medical outcomes observed following coexposure were 7.7% in the low dose group, 44.4% in the moderate dose group and 42.9% in the high dose group with an increase in kratom dose (Table 3). Coexposures accounted for an increased rate of ICU admission (28.3% vs. 8.6%; 95% CI: 1.5–7.1, $p<0.01$). The chronicity of kratom exposure did not result in a significant difference in major medical outcomes (15.9% vs. 16.7% in acute vs. chronic exposure; 95% CI: 0.3–2.9).

In the major medical outcome subgroup, 14 subjects had CNS depression, which accounted for most symptoms, and nine required intubations. Four subjects (28.5%) with this presentation did not report a history of coexposure (Supplementary Table 1). Naloxone was given to 21 patients in both hospital and prehospital settings. Eight patients (38%) in the major medical outcome group were noted to be obtunded with or without respiratory depression. Most of them, who did not report a history of other opioid use, dramatically regained consciousness after a single dose of naloxone. Eight subjects who were intubated were successfully extubated several days later without apparent sequelae. The only reported fatality in our study was a 41 year old man who consumed an unknown amount of kratom capsules and reported the use of opioid based pain medication. He was intubated and then developed renal failure, liver failure, and severe metabolic acidosis, with an ICU length of stay of 4 days before death (**Table 4**). One patient who developed severe rhabdomyolysis (CK>50,000 U/L), hepatic failure and renal failure was lethargic at the initial presentation, while two other patients who had mild to moderate rhabdomyolysis experienced a period of increased muscle activity (serotonin syndrome or seizure) and agitation.

Table 4: Details of major clinical outcome cases

	Exposure	Dose in 24 h	Coexposure	Effects	Treatment
36-year-old M	Oral abuse	Capsule unknown dose	None	Rhabdomyolysis (CPK > 50,000), liver failure, renal failure	Hemodialysis, sodium bicarbonate
47-year-old M	Withdrawal	4–5 tablets, stopped using for 3 days	None	Seizure, acidosis	Hemodialysis, sodium bicarbonate
28-year-old M	Oral abuse	Powder unknown dose	None	Unresponsive	Naloxone, oxygen
30-year-old M	Oral abuse	Capsule unknown dose	None	Hallucination, seizure, rhabdomyolysis (CK 9,588)	Antipsychotics, benzodiazepine
18-year-old M	Oral abuse	Capsule unknown dose	None	Unresponsive	Intubation, sedation
29-year-old M	Oral abuse	Capsule unknown dose	None	Lethargic, unresponsive	Naloxone
18-year-old M	Oral abuse	Capsule unknown dose	None	Lethargic, unresponsive, apneic	Naloxone, intubation, sedation
41-year-old M	Oral abuse	Capsule unknown dose	Opioid-based pain meds	Lethargic, acidosis, liver failure, renal failure, death	Intubation, sedation, antibiotics, pressors, hemodialysis
55-year-old M	Smoked plant material	4 tablets	Blood thinners	Massive GI bleeding, hypotension, tachycardia	Intubation, pressors
60-year-old F	Oral abuse	Tablets unknown dose	Aripiprazole, escitalopram	QT prolongation, torsade de pointes, lethargic	Intubation, sedation, antiarrhythmic, pressors
24-year-old M	Oral abuse	Unknown	Escitalopram	Serotonin syndrome, agitation, rhabdomyolysis (CK 2,300)	Intubation, sedation
20-year-old M	Suspected suicide	Unknown	Lorazepam, gabapentin	Unresponsive, apneic	Intubation, sedation
47-year-old M	Oral abuse	Capsule unknown dose	Lithium	Lethargic, unresponsive	Naloxone, oxygen
60-year-old M	Suspected suicide	60 tablets	Clonazepam	Lethargic, unresponsive	Naloxone, oxygen
57-year-old M	Oral abuse	Capsule unknown dose	Aspirin, ethanol, duloxetine	Agitation, combative, myoclonus	Benzodiazepine, sedatives (others)
18-year-old M	Oral abuse	Capsule unknown dose	Dextromethorphan	Seizure (at home), unresponsive	Supportive care
20-year-old M	Suspected suicide	17.5 gram	Clonazepam, pregabalin	Unresponsive, apneic	Naloxone, oxygen
57-year-old F	Suspected suicide	Capsule unknown dose	Baclofen, nortriptyline	Lethargic, unresponsive, QRS widening	Intubation, sedation, sodium bicarbonate
48-year-old M	Suspected suicide	> 20 tablets	Quetiapine	Seizure	Intubation, sedation
32-year-old M	Oral abuse	12–15 capsules	Benzodiazepines	Unresponsive	Naloxone, benzodiazepine, sedatives (others)
33-year-old F	Suspected suicide	15 capsules	Acetaminophen	Unresponsive	Naloxone
26-year-old M	Oral abuse	15 capsules	Benzodiazepines	Tachycardia, agitation	Antipsychotics, intubation, sedation
34-year-old F	Oral abuse	20 tablets	Benzodiazepines	Lethargic, unresponsive	Intubation, sedation

Discussion

This study provides novel information concerning the characteristics and medical consequences of kratom use in the southeastern region of the US based on data obtained from the GPC and APIC. In most states in the US, kratom is legal, and there are no laws or pending legislation to prohibit its sale or possession. However, Alabama is one of the few states where kratom is illegal. Our research provides an analysis of exposure to kratom alone and together with pharmaceutical drugs. This work contributes to the current knowledge of the clinical effects of kratom exposure and may help to guide future studies on this substance.

The alkaloids mitragynine and 7-HMG are the main active substances in this plant [13], and research has demonstrated dose dependent CNS stimulant and sedative effects [1]. Regarding the opioid like effects of kratom, mitragynine is approximately 13 times more potent than morphine, while 7-HMG, which accounts for up to 2% of the total active ingredients [14], is 4 times more potent than mitragynine in terms of CNS stimulation and depression

[15]. An in silico binding profile study demonstrated that kratom alkaloids share structural features with controlled opioids, revealing several alkaloids that bind receptors in the CNS [16]; a higher dosage reflects exposure to more active compounds [17]. Previously published national data revealed that neurological symptoms are variable but common following kratom exposure [3]. While sedative and simulant effects were observed in the patients with kratom only exposure, these effects were not dose dependent in our study. The kratom dose, type of kratom product and heterogenicity of such products might affect the clinical symptoms presented [18] and depend on the concentration of alkaloid substances present in the leaves, which varies by strain. The legal status of kratom across states also impedes efforts to standardize commercial kratom preparations [19]. Our study did not show an increase in ICU admissions or major effects in a dose dependent manner in subjects who consumed more than moderate doses of kratom (>5 g).

Although kratom is classified as an herbal supplement, it can induce harmful physiological responses [20]. Previous studies have noted a mild stimulant effect after exposure to 1–5 g of kratom. At these low doses, unwanted side effects have been described but are generally minimal. Some patients who consumed more than 15 g of kratom reported stupors similar to those obtained from opioids [13]. The elevated blood pressure observed in the low dose kratom group could be explained by kratom's adrenergic effect. However, without adjusting for age or history of hypertension, this observation precludes any firm conclusions regarding this result. Other common symptoms observed in our study were nausea, vomiting, palpitation and tachycardia. Unintentional pediatric exposures are uncommonly associated with severe clinical effects [21]. Our data showed that all unintentional pediatric exposures (n=7) required only a brief observation in an emergency department.

Unusual manifestations of kratom exposures reported in this study included seizures (n=5), elevated transaminases (n=2) and increased bilirubin levels (n=1), supporting the concerns over kratom related toxicities described in previous reports [22-24]. From our chart review, patients who present with major CNS depression may not have respiratory depression, which is inconsistent with the classic opioid toxidrome. This finding is concordant with reports from previous studies showing that respiratory depression is uncommon with mitragynine compared to other opioids [25,26]; however, there is no clear guidance on how they should be treated.

The NPDS database reported that kratom is associated with a variety of serious medical outcomes, especially when used with other substances [3]. Although we excluded drugs of abuse and limited our coexposure samples to the therapeutic use of pharmaceutical drugs, we observed more severe effects with coexposure. Phase-I and phase-II metabolizing enzymes are responsible for mitragynine metabolism, although one systematic review on the pharmacokinetics of mitragynine mentioned that the studies differed in terms of their reporting, reliability, and completeness and that the data on metabolism and excretion cannot be applied to humans [27]. Mitragynine can inhibit CYP2D6 and can weakly inhibit some other CYP enzymes, which could result in interactions with other prescriptions and over the counter drugs [28]. This point may contribute to our finding that patients with kratom exposure involving multiple substances had higher risks of hospital admissions and serious medical outcomes, consistent with some previous studies [13,18].

Because most kratom users usually do not consume only kratom, some of the adverse health effects associated with its use may be caused by other substances or may be exacerbated by pre-existing health conditions [29]. Adulteration is a concern because serious adverse effects or even death may result [1,13]. The current literature suggests that kratom may sometimes contain carisoprodol, modafinil, diphenhydramine, Datura stramonium, fentanyl, caffeine, morphine, or tramadol. This finding can be applied to our patients who had dramatic responses to naloxone, as these patients may have consumed other opioids in addition to the kratom. Review articles recommend the administration of naloxone in the case of opioid toxidrome from kratom overdose [30]; however, it should be noted that the clinical effectiveness of naloxone has not been proven. In a previous study, kratom only exposure did not influence the QTc interval, but a nonsignificantly higher incidence of QTc prolongation was found in subjects who used kratom along with other xenobiotics [31]. This result was also found in our study.

Recently, kratom has seen a surge in demand among products marketed to be alternatives to opioids for pain control and to ameliorate opioid withdrawal symptoms. The current human pharmacological, pharmacokinetic, and clinical data are of low quality, so firm conclusions regarding the safety and efficacy of kratom cannot be drawn. Our report supports the call for additional studies to explore potential health hazards associated with kratom exposure and whether regulatory oversight is necessary

Study limitations

This study has several limitations. The cross sectional design of this study did not permit assessments of the causal relationships between various factors and the occurrence of medical outcomes. A well-controlled study with known doses/weight/timing is needed to investigate a dose effect relationship, which is not possible with PCC data [32]. The clinical symptoms of kratom exposure are not well defined; thus, some clinical effects that are not known to be caused by kratom exposure may not be documented. Exposure was established according to medical history, and laboratory test results, which were not part of the inclusion criteria, were not recorded for most patients. Some subjects could not provide an exposure history or quantitative substance information because of mental alterations or unwillingness to provide complete information due to the fear of negative ramifications.

Conclusion

Kratom exposure is associated with a wide range of neu-

rological and cardiovascular effects. However, due to the safety and lack of quality control of kratom products sold in the US, the probability of more severe symptoms and serious effects should be considered, particularly when kratom is used with other medications. Subjects with concerning symptoms should be sent to a healthcare facility for evaluation and observation of possible side effects

Conflict of Interest Disclosure

We declare that we have no conflicts of interest related to the authorship or publication of this manuscript.

Data Availability Statement

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

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