

Kratom Related Adverse Event Reports from the FDA CFSAN Adverse Event Reporting System (CAERS), 2021



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Introduction

- Kratom (*Mitragyna speciosa*) is a tropical evergreen tree native to Southeast Asia. Its leaves contain two major psychoactive ingredients (mitragynine and 7-hydroxymitragynine).
- In recent years, kratom has gained popularity in Western countries as a plant-based novel psychoactive substance ([Nsubuga et al., 2022](#)).
- Kratom, which affects the same opioid brain receptors as morphine, poses risks of addiction, abuse, and dependence ([Anwar et al., 2016](#)).
- Currently, kratom products are neither approved for any therapeutic use nor regulated on a federal level in the U.S.
- The U.S. Food and Drug Administration (FDA) is actively evaluating scientific information about the safety of kratom and has warned consumers not to use kratom products (<https://www.fda.gov/news-events/public-health-focus/fda-and-kratom>).
- The FDA CFSAN (Center for Food Safety and Applied Nutrition) Adverse Event Reporting System (CAERS) is a post-marketing surveillance system that receives and monitors adverse event (AE) and product complaint (PC) reports for foods, dietary supplements, cosmetics, and infant formula.
- Many data gaps exist regarding the safety of kratom products. Review of adverse event reports related to kratom products may help increase our understanding of potential health effects associated with kratom.

Photo Examples of Kratom Products



Liquid Extract

Powder

Capsules

Materials and Methods

CAERS receives adverse event reports via MedWatch, Safety Reporting Portal (SRP), Field Accomplishments and Compliance Tracking System (FACTS), emails, and telephone calls. Adverse events are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA). One CAERS adverse event report can have multiple outcomes.

We queried the CAERS database for reports that contain the following key words in product names, ingredients, or narratives: kratom, mitragyna speciosa, mitragynine, biak-biak, cratom, gratom, ithang, kakuam, katawn, kedemba, ketum, krathom, krton, mambog, madat, Maeng da, nauclea, nauclea speciosa, or thang. We extracted the CAERS ID, age, sex, ethnicity, race, outcomes, symptoms, CFSAN product type, and System Organ Classes (SOCs). We assessed the reports and provided descriptive statistics.

Results and Discussion

- In 2021, CAERS received 78 reports involving kratom products. The majority of reports (96%) noted at least one adverse event. Thirty-seven (47%) reports were submitted by a consumer, 31 (40%) by friend/relative of consumer, 9 (12%) by a health care professional, and 1 (1%) by law enforcement.
- Of the 78 kratom reports received, 45 (58%) were adverse events only, 3 (4%) were product complaints only, and 30 (38%) were for both adverse events and product complaints (**Fig. 1**).

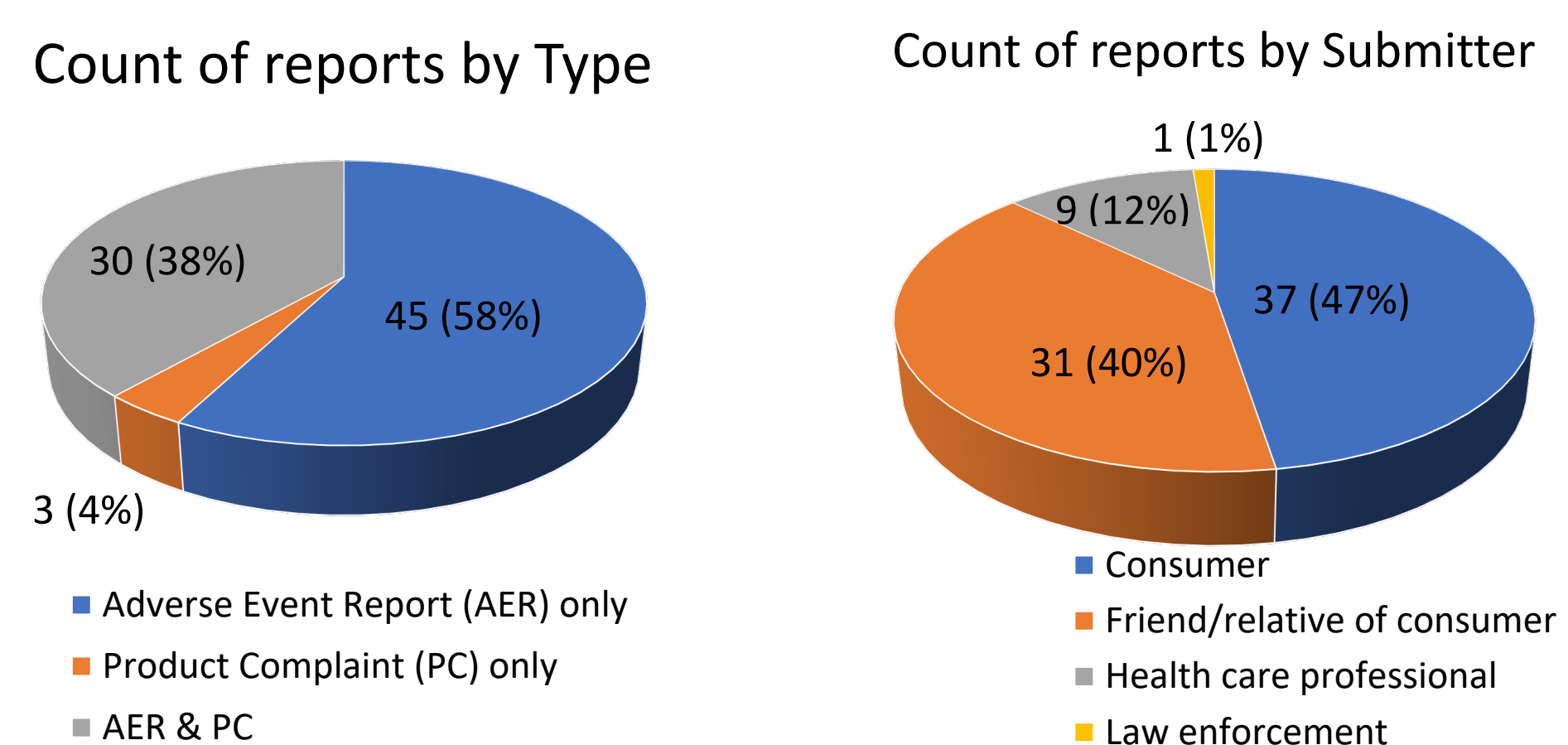


Figure 1. Count of kratom reports CAERS received in 2021 by report type and report submitter.

- Next, we performed a descriptive analysis of the kratom reports CAERS received in 2021 (**Table 1**). All reports were related to adults with a mean age of 36, a media age of 39, and an age range of 21 to 69 years old. The majority of the reports involve male (72.6%).

| | | |
|------------------------------|---|---------|
| Age (years) (n=65) | Median | 36 |
| | Mean | 39 |
| | Range | [21-69] |
| Sex (n=73) | Female | 20 |
| | Male | 53 |
| | | |
| | | |
| Race* (n=64) | Asian | 1 |
| | Black or African American | 2 |
| | White | 62 |
| | Native Hawaiian or Other Pacific Islander | 1 |
| Ethnicity (n=55) | Hispanic/Latino | 3 |
| | Not Hispanic/Latino | 52 |
| Outcomes** (n=75) | Death | 20 |
| | Disability | 15 |
| | Hospitalization | 20 |
| | Life threatening | 12 |
| | Medically important | 38 |
| | Patient visited ER | 3 |
| | Patient visited healthcare provider | 4 |
| | Other seriousness | 1 |

*A complainant can identify with more than one race.

**A complainant can have one or more outcomes.

Table 1. Descriptive Characteristics of kratom CAERS reports.

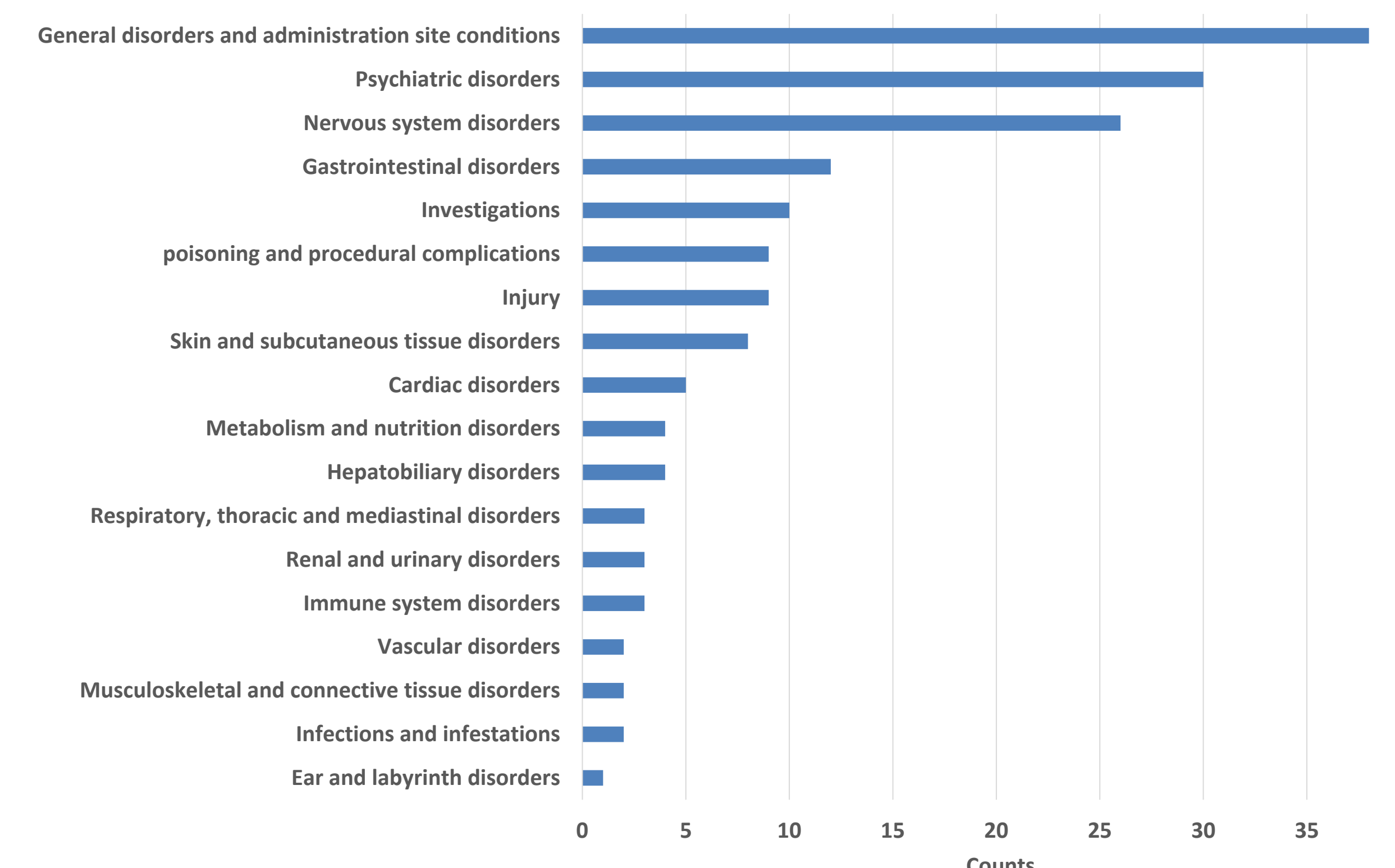
MedDRA "Preferred Term" is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. A complainant can describe multiple adverse events that include multiple PTs. The 6 most common PTs reported for kratom reports were death, dependence, convulsion, malaise, anxiety, and withdrawal syndrome (**Table 2**).

| Preferred Terms (PTs) | Counts |
|-----------------------|--------|
| Death | 20 |
| Dependence | 19 |
| Convulsion | 13 |
| Malaise | 8 |
| Anxiety | 7 |
| Withdrawal syndrome | 7 |

*Shows only PTs with counts ≥ 7

Table 2. Summary of MedDRA "Preferred Terms (PTs)" for 2021 kratom CAERS reports (n=75)

- Summary of System Organ Class (SOC) for the adverse events involving kratom products from 75 adverse event reports indicated these adverse events span a wide range of organ systems (**Figure 2**).



*A complainant can describe multiple adverse events that span multiple SOCs.

Figure 2. System Organ Classes (SOCs) for kratom adverse event reports (n=75).

- Regarding the reason for use, there were 53 reports in which the complainants self-reported at least one condition for kratom products. In terms of frequency, the top four reasons for using kratom products reported were for pain, anxiety, depression, and opioid/heroin withdrawal (**Figure 3**). A consumer can have multiple reasons for using the kratom products.

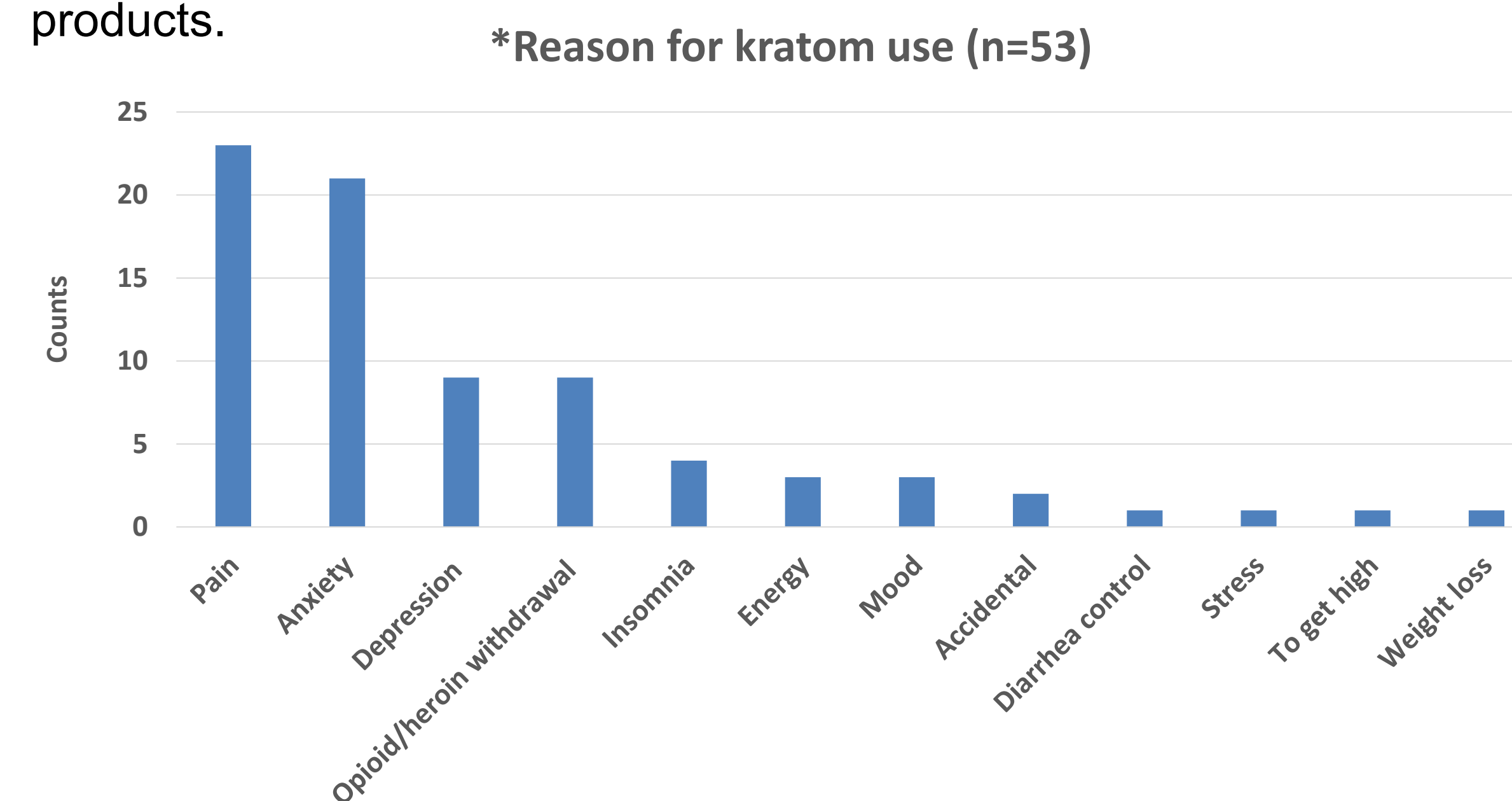


Figure 3. Reasons why consumers used kratom products (n=53).

- Results of medical examination and toxicology testing were obtained for 10 death reports. Mitragynine toxicity was listed as the sole cause of death in 4 cases (40%), and a contributory factor in the other 6 cases (60%). The blood mitragynine concentration in the 10 death reports ranged from 190 to 5,400 ng/mL (**Table 3**).

| Case | Age, y/Sex | Cause of death (reported by Medical Examiner) | Blood mitragynine level | Other substances detected |
|------|------------|---|-------------------------|--|
| 1 | 38/Male | Not on tox report | 4500 ng/ml | promethazine |
| 2 | 42/Male | acute mitragynine toxicity | 620 ng/mL | caffeine, 7-amino clonazepam, lamotrigine, paroxetine |
| 3 | 27/Male | acute mitragynine toxicity | 2100 ng/mL | caffeine, cotinine, naloxone (administered by EMS) |
| 4 | 28/Male | fentanyl and mitragynine toxicity | 190 ng/ mL | caffeine, 7-amino clonazepam, delta-9 carboxy THC, delta-9 THC, fentanyl, norfentanyl, cannabinoids |
| 5 | 38/Male | mitragynine toxicity | 2700 ng/mL | no other substances noted |
| 6 | 27/Male | acute mitragynine toxicity and hypertensive atherosclerotic disease | 1900 ng/mL | paroxetine, caffeine, cotinine (nicotine metabolite), isopropranol (likely contaminant from organ procurement per coroner) |
| 7 | 38/Male | venlafaxine and mitragynine overdose | 3100 ng/mL | caffeine, naloxone, 7-Amino, clonazepam, venlafaxine, O-desmethylvenlafaxine, doxepin, Desmethyldoxepin, |
| 8 | 31/Male | acute toxicity of mitragynine and alcohol | 290 ng/mL | sertraline, ethanol, mirtazapine, zopiclone, lorazepam |
| 9 | 35/Male | acute mitragynine toxicity | 5400 ng/mL | citalopram, diphenhydramine, nicotine |
| 10 | 27/Male | complications of mitragynine toxicity | 1500 ng/mL | codeine, benzoylcegonine (cocaine metabolite), cotinine (nicotine metabolite), caffeine, naloxone |

Table 3. Toxicology Data from 10 death reports involving kratom products.

Conclusions

- In 2021, CAERS received 78 reports involving kratom products. The majority of reports (96%) noted at least one adverse event.
- The 6 most common PTs reported for kratom were death, dependence, convulsion, malaise, anxiety, and withdrawal syndrome.
- The top four reasons for using kratom products reported were for pain, anxiety, depression, and opioid/heroin withdrawal.
- Kratom use, most often in combination with other substances, can be associated with serious adverse events including death.
- Review of CAERS adverse event reports may help provide real-world data to understand the safety of kratom products