Kratom has come, gradually, to BC:
Cases managed by the British Columbia poison centre, 2012-2019

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ABSTRACT

Background:

Kratom, a plant indigenous to Southeast Asia, has been used both recreationally and in the treatment of pain and opioid dependence. While kratom has so far received little attention in North America and almost none in Canada, US studies suggest that although kratom use is increasing, severe effects are infrequent.

Methods:

Our observational case study used kratom-specific substance codes and a verbatim search to identify exposures managed by the British Columbia (BC) Drug and Poison Information Centre (DPIC) from 2012 – 2019. We examined trends in exposures, reasons for exposure, concurrent drug exposures and clinical outcomes.

Results:

32 cases were identified. In 23 (72%) cases, DPIC was consulted by a healthcare worker. Case numbers increased from 0 in 2012 and 2013 to 9 in 2019. Case numbers were highest for males in their twenties (17 [53%]). Almost all cases involved ingestion, with online distributors and local stores listed as sources of procurement. A co-exposure substance was identified in 13 (41%) cases. There were no deaths; in one case, the exposed individual was intubated to manage agitation following kratom withdrawal.

Interpretation:

This is the first synthesis of kratom exposures managed by a Canadian poison centre. The steady increase in kratom-related poison centre calls, especially in young adult males, may reflect increasing availability. Increased use may also be a consequence of BC's opioid crisis with kratom used to lessen opioid withdrawal symptoms. Still, most exposure/withdrawal cases have been mild-to-moderate in severity. Queries of DPIC by BC clinicians indicate that they remain largely unaware of the nature and effects of kratom. Our BC findings should inform the development of regulations for the prescription, marketing and use of kratom.

Introduction

Mitragyna speciose, commonly known as kratom, is a tree indigenous to Southeast Asia used in traditional medical practice. Historically, kratom leaves have been brewed into tea and used as a herbal stimulant and analgesic as well as a remedy for hypertension, diarrhea, and opioid dependence.[1,2] The effects of kratom appear to be dose-dependent, with stimulatory effects at lower doses and sedative, opioid-like effects at higher doses.[1] Kratom leaves contain mitragynine and related alkaloids likely responsible for its psychotropic effects.[3] Adverse effects of kratom include nausea, vomiting, and liver toxicity.[4] During withdrawal, habitual users may experience insomnia, agitation, myalgia and seizures.[3,5]

Today, kratom leaves are dried and formulated into powders and pills which have recently become available and popular in western countries. From 2010-2015, United States poison centres experienced a tenfold increase in calls about exposure to kratom;[6] while most calls were not associated with severe medical outcomes, cases of psychosis, seizures, and respiratory depression have been reported,[6,7] particularly when kratom was consumed with other substances.[8,9,10,11,12] A New York county medical examiner reported four kratom-related deaths from 2011-2018 of which two involved co-exposures and two no concurrent drug exposures.[13]

In Thailand, kratom has been illegal to buy, sell, or possess since 1943.[14] In Canada, kratom is currently not a controlled substance and its possession and consumption are not illegal. However, it is illegal to sell kratom for human consumption. Despite this, kratom has become widely available through both online and local distributors where it is marketed as "Not Consumable."[15,16]

There are many case reports of individuals using kratom as a substitute for opioids or as treatment for opioid withdrawal.[17,18,19] Since 2014, British Columbia (BC, Canada), has seen a marked rise in opioid overdoses following the substitution of heroin and pharmaceutical opioids with fentanyl and its derivatives.[20] Given kratom's toxicity and that at high doses it has psychotropic effects similar to opioids, awareness of the use of kratom in BC is important.

Methods

Data accessed and study design:

We reviewed calls to the BC Drug and Poison Information Centre (DPIC) involving exposure to kratom between 2012-2019. DPIC provides free drug and poison information and management support to both the BC public (2016 population 4.6 million) and, through a dedicated line, to the province's clinicians. Phone calls are managed by nurses and pharmacists with certification from the American Association of Poison Control Centers (AAPCC).[21] Call information is collected through a series of drop-down, data-coded, and narrative text fields and is stored in a database using Visual Dotlab® patient management software designed for poison centres.[22] A kratom case was defined as an individual whose exposure led to a call to DPIC. Cases were extracted using Poisindex® product codes 7224390 Kratom and 4271683 Plants: Mitragyna and AAPCC generic substance code 310130 Kratom.[21,23] Cases were also identified from all exposure calls without those three substance codes by searching for "kratom" in the non-coded "substance verbatim" field. Finally, we identified cases AAPCC-coded as generic substances 93000 Plants: Hallucinogenic and 97686 Plants: Other Toxic, and searched narrative text fields for "kratom" and/or "mitragyna."[21] Calls in which an individual was only seeking information on kratom and where there was no exposure were excluded, as were calls for information by a health care professional in advance of a patient consultation.

Coded fields assessed included age and sex of the individual exposed, caller relationship to the exposed individual (physician, pharmacist, friend/parent, self), date of exposure and call, route of exposure, reason for call (adverse reaction, toxicity, withdrawal), acute versus chronic use of kratom and medical outcome. Medical outcomes for cases were classified as minor, moderate, or major as determined by National Poison Data System (NPDS) classification based on clinical effects.[24] Minor outcome was the typical description of a patient with minimal symptoms as a result of the exposure who returned quickly to a pre-exposure state, moderate outcome usually involved some need for medical care but expected to resolve without complication, and major outcome involved a life-threatening condition or resulted in serious residual morbidity in which significant medical intervention (e.g., intubation) would be expected. Location of call was recorded and classified as urban, mixed urban/rural, or rural based on BC's Health Service Delivery Areas rurality index.[25] Clinical care trajectory (managed at home, treated/evaluated at

health care facility) associated with the exposure was also classified from the coded information. Case narrative notes were reviewed by two authors (NR and TK) and compared to coded fields to verify their accuracy and to create new fields not part of the Visual Dotlab® case record. These additional fields included reason for kratom use (therapeutic for pain, opioid withdrawal, reason unclear), amount of kratom used in grams, concurrent exposure substances and source of kratom (online, local distributor). The text was also reviewed to extract symptoms, signs, and treatment location.

To address the dose-dependent nature of kratom, cases where symptoms included respiratory failure, coma, or drowsiness were labelled as "depressive effect" and cases with nausea, vomiting, anxiety; tachycardia, headache and/or dizziness were classified as "stimulant effect." Cases where the patient had discontinued kratom use for >12 hours following preceding long-term exposure, and had symptoms including nausea, myalgia, diaphoresis, diarrhea, tremors, agitation and/or anxiety were labelled as "kratom withdrawal." Cases where the patient presented primarily with abdominal pain, jaundice, pruritus and/or discolored urine and where there was evidence of hepatotoxicity such as elevated liver enzymes, bilirubin and/or evidence of biliary tree changes on imaging were labelled as "hepatotoxic effect."

DPIC also receives opioid-related exposure calls. We accessed these calls using a cluster of AAPCC codes.* We compared numbers of kratom and opioid exposure cases by year.

Statistics

Data was analysed and figures drawn in Microsoft Excel.[26] Equivalence of medians was tested with the non-parametric Wilcoxon rank sum test, and contingency tables were tested with the Fisher's exact test.[27]

Research ethics

The BC Centre for Disease Control Data Access and Privacy Officer informed that ethics approval was not required given that the data did not contain identifying features and was used for surveillance purposes.

* 72696, 72699, 72700, 201063, 72704, 72702, 72703, 72716, 72713, 72691, 72694, 41696, 41699, 41700, 41707, 41706, 41718, 41691, 41694, 200634, 26000, 77832, 37830, 37784, 37786, 37780, 37782, 200625, 200626, 37701, 200635, 200627, 200628, 37702 ,200629, 200630, 201066, 37707, 37703, 37704, 200636, 41715, 41712, 37708, 77810, 37705, 200632, 37706, 78701, 200638, 200637, 200633, 201131

Results

Cases per year, and case characteristics

We identified 35 cases of kratom exposure between 2012-2019 including one where "kratom" was noted in the substance verbatim field. There were no repeat exposures. In three cases, a health care professional called DPIC to get general information on kratom in advance of a patient consultation. These cases were not included in our analysis, giving a total exposure count of 32, or 0.086 kratom exposures/year per 100,000 (2016) BC residents. There were no cases in 2012 or 2013 and case numbers increased steadily from 2014-2019 (Figure 1).

Age was recorded as "adult – age unknown" in four cases; median age of the 28 remaining cases was 25.5 and 19 (68%) cases were aged 20-39. There were 2 cases in adolescents 17 and 18, and 4 cases over 50 years old. 25 (81%) cases involved a male (Figure 1). Median age of male cases was 25.5 and the median age of female cases was 40 ($p=0.25$, Wilcoxon rank sum test).

21 (66%) cases were from metropolitan areas, 6 (19%) from mixed/urban settings and 5 (16%) from rural/remote areas versus 56%, 32% and 12% of BC's population, respectively ($p=0.09$, Fisher's exact test).

Of 32 calls, exposed persons, family and friends made 9 (28%), 19 (59%) were from physicians and 4 (13%) from other healthcare workers (nurses, emergency health technicians). 19 calls (59%) originated in hospitals. Physicians asked about potential drug interactions, interpretation of laboratory analyses and treatment of toxicity or withdrawal in their patients (Figure 2).

Source, dose, co-exposures

Sources of kratom procurement volunteered to DPIC included online distributors [5 (16%)] including one listed as "Kratom Canada" and one local walk-in store. Most calls [26 (81%)] did not volunteer the source. Ingestion was by far the most common exposure route [27 (84%)]); in 4 (13%) cases the route was not listed and there was one case of parenteral use. Of the cases where the form of ingested kratom was recorded, 3 (17%) were liquids/tea, 6 (33%) were powder, one was leaves, and 8 (44%) were tablets.

There were 9 cases where the amount of kratom used was recorded. In 4 cases of chronic use, dose ranged from 3–20g/day. Dose in 5 acute exposures ranged from 3–70g.

13 cases involved co-exposure to substances including alcohol, marijuana, benzodiazepines and others (Table 1). In only one case was concurrent exposure to an opioid (in that case poppies) noted. In 19 cases, no co-exposure substances were noted.

Table 1: Kratom-related cases reported to the British Columbia Drug and Poison Information Centre where a concurrent exposure was identified, 2012-2019

Co-Exposures	Number (%) of Cases
Only kratom identified	19 (59%)
Co-exposure recorded:	13 (41%)
· Alcohol	4
· Marijuana	3
· Benzodiazepines	3
· 3-Fluorophenmtrazine	1
· 5-HTP	1
· Acetaminophen	1
· L-Tyrosine	1
· Dextroamphetamine tea	1
· MDMA	1
· Phenibut	1
· Maca Root	1
· Opium Poppies	1

Circumstances of use

In 24 (75%) cases, the use of kratom was intentional although the nature of intent was not explicit. Pain control [5 (16%)] and self-treatment for opioid withdrawal [3 (9%)] were the two other specified reasons for kratom use. There was no observed trend in reasons for kratom use over the study period.

15 (57%) cases involved chronic exposure (>21 days) to kratom while in 14 (44%) cases, exposure was acute; in 3 (9%) use duration was not recorded.

Clinical trajectory

Most cases [24 (75%)] concerned kratom toxicity; however, 8 (25%) cases involved a chronic user who was experiencing symptoms of kratom withdrawal after discontinuing its use.

Stimulant effect was the most common clinical presentation and cases with symptoms of withdrawal were also frequent (Table 2).

Table 2: Clinical presentations of kratom exposure cases reported to the British Columbia Drug and Poison Information Centre, 2012-2019

Clinical Presentation	Number (%) of Cases
Stimulant Signs/Symptoms	14 (44%)
Depressive Signs/Symptoms	4 (13%)
Hepatotoxic Signs/Symptoms	4 (13%)
Withdrawal Signs/Symptoms	8 (25%)
Could not classify	2 (6%)

In 3 (9%) cases, the person exposed was advised to go to hospital. In 8 (25%), the call concerned a patient admitted to hospital (7 to non-critical care, 1 to critical care). In 10 (31%) cases the patient was managed outside of hospital, 7 where the exposed person was at home and 3 where they were managed in a physician's clinic. 11 (34%) cases were released from the emergency department after evaluation/treatment.

13 (36%) cases were considered to have minor outcomes, 15 (42%) moderate and 1 major. There were no deaths. In 3 (9%) cases the medical outcome was not recorded. The one major outcome involved intubation for control of agitation secondary to kratom withdrawal. There was no association of the ratio of minor to moderate outcomes in cases who were exposed to other substances *versus* cases who were not exposed to substances other than kratom (Figure 3).

In 13 (41%) cases, there were 1 or more follow-up calls by DPIC. Of the 13 follow-ups, 3 involved non-hospitalized individuals managed at primary care offices and 10 were follow-ups on hospitalized patients; there were no follow-ups on exposed individuals managed at home.

Kratom and opioids

DPIC cases related to opioid use remained elevated throughout 2012-2019 and peaked at 965 in 2015, while kratom cases increased steadily from 2014 to 2019 (Figure 4).

Interpretation

Poison centre records capture exposures to harmful substances. While several reports of kratom exposure and its consequences have been based on poison centre records, we were unable to identify any that referenced hospital visits, related perhaps to the absence of a specific International Classification of Diseases code for kratom.

A review of kratom cases from Thailand's Ramathibodi Poison Center identified 52 managed from 2005-2009.[14] A case series from the Virginia Poison Center identified a kratom call as early as 2002.[28] 14 exposures were described in a study that included five Texas poison centers for the years 2009-2013.[29] Three reports, based on calls to all US poison centers uploaded into the NPDS described sharply rising call numbers over the period 2010-2017.[6,7,13] The most comprehensive pan-US report enumerated 1807 exposure calls from 2011-2017.[7] More serious outcomes were associated with exposure to kratom along with other substances.[7] While these US reports provide insight into trends in kratom use, a limiting feature is that none accessed information beyond mandatory NPDS fields.

Of note in our review of kratom cases managed by the BC Drug and Poison Information Centre is that: DPIC is the sole source of poison information and management for British Columbia ensuring complete capture of all calls from BC residents; besides helping to manage exposures, DPIC has a drug information line with dedicated access for practitioners; DPIC has maintained an electronic database since 2012. Compilations of reports from several poison centres, as in the 2013 Texas review, or the 2016 and 2019 reviews of all cases managed by 42-plus US poison centres, with the variety of data platforms they use, are unlikely to match the consistency in soliciting and recording of information that characterizes DPIC records.[6,7,13,28,29]

Kratom came late to BC as compared to Thailand, Malaysia and Myanmar where it has long been in use and is illegal. While in the US, cases were noted as early as 2002, besides our 2018 scan of DPIC cases[30] only two Canadian case reports of kratom use have been published.[15,16] Our series of 32 cases shows that while calls around the use of kratom are increasing, characteristics associated with its use are similar to those described in the US:

- Exposure rates were highest in the US northwest including 3.8/million/year in Oregon and 3.9 in Idaho between 2011-2017.[7] Our study showed an annual exposure rate of 0.86/million/year.
- In our study, the median age of cases was 25.5 years, comparable to the US Center for Disease Control study of 660 cases with a median age of 28 years. Of cases where sex was recorded, 81% were males compared to 79% in the US.[6]
- Almost all BC cases involved ingestion as the exposure route, either through powder, capsules or tea which is consistent with US findings.[6,29]
- There were slightly more cases of kratom use alone compared to use with other substances; the most common co-exposures were alcohol, benzodiazepines and other botanicals such as marijuana. Both findings were consistent with US poison centre reports.[6,7,28]

Our study differed from other poison centre reviews in the incorporation of case notes which offered insight into reasons for kratom use. Most often this was recorded or coded as "intentional". We did identify a fraction that used kratom specifically for pain and a smaller fraction for opioid withdrawal. Reference to case notes also revealed that in BC, kratom is sourced both locally and online. Rising exposure rates may reflect the recent ease of access to online distribution. Using case notes, we were also able to classify clinical presentations as hepatotoxicity, kratom withdrawal, stimulant effect, or depressive effect. Hepatotoxicity was frequent among BC cases and the most common clinical presentation was stimulatory effect.

Despite case reports in the BC and Canadian Medical Association Journals[30,31] as well as local press coverage,[32] DPIC continues to receive inquiries from clinicians largely unaware of kratom and its effects. 72% of the DPIC case calls were from health care workers, similar to US studies. As for management site, one pan-US review of 1566 kratom exposures found that 9.6% were managed outside hospital[7] compared to 31% of cases in BC that were managed outside hospital (at a clinic or at home). Comparing clinical outcomes, BC had a larger percentage of moderate outcomes than the pan-US poison center study (52% vs 43%) and fewer major outcomes (3% vs 9%).[7]

An ongoing opioid crisis exists in BC, largely associated with the substitution of fentanyl and its derivatives for other opioids. Over the period 2012-2019, exposures to kratom, sometimes used

to mitigate opioid withdrawal, appear to be minuscule, and with lesser consequences than opioids. Still, we might expect kratom to be used increasingly by individuals wishing to curb opioid use.

In Canada, while the sale of kratom for consumption is illegal, clearly it is sold and consumed. Our review yielded few severe outcomes among the 32 exposed persons. Lacking surveys of kratom use in BC, estimates of 10-16 million current regular US users might suggest that 100,000 or more BC residents use kratom.[33] If accurate, we could estimate that only a small fraction of BC exposures results in poison centre calls and that a much smaller fraction is associated with serious effects on health.

There are limits to the comprehensiveness and quality of the information we gathered from poison centre records. It is possible that exposure to kratom was not specifically named by callers and that poison centre staff recorded cases as exposures to "plants" or "hallucinogens." Additionally, the DPIC record of exposure to kratom was not validated by assessment of the substance consumed or by biological sample. Furthermore, there was little information regarding dose. We were also limited in understanding the source and means of exposure, relying on information volunteered by users or caregivers. Lastly, it was difficult to attribute symptoms to kratom in cases of polysubstance use.

Conclusion

Poison centre records inform the surveillance of population exposures to potentially harmful substances. Our review of eight years of calls to the BC poison centre about exposure to kratom shows increasing numbers, driven by ingestions in young adult men. This may reflect both increased availability and kratom's use to mitigate opioid withdrawal. Still, serious adverse events are infrequent. As exposures continue to rise, it is important that health care professionals and regulators are aware of kratom and its effects.

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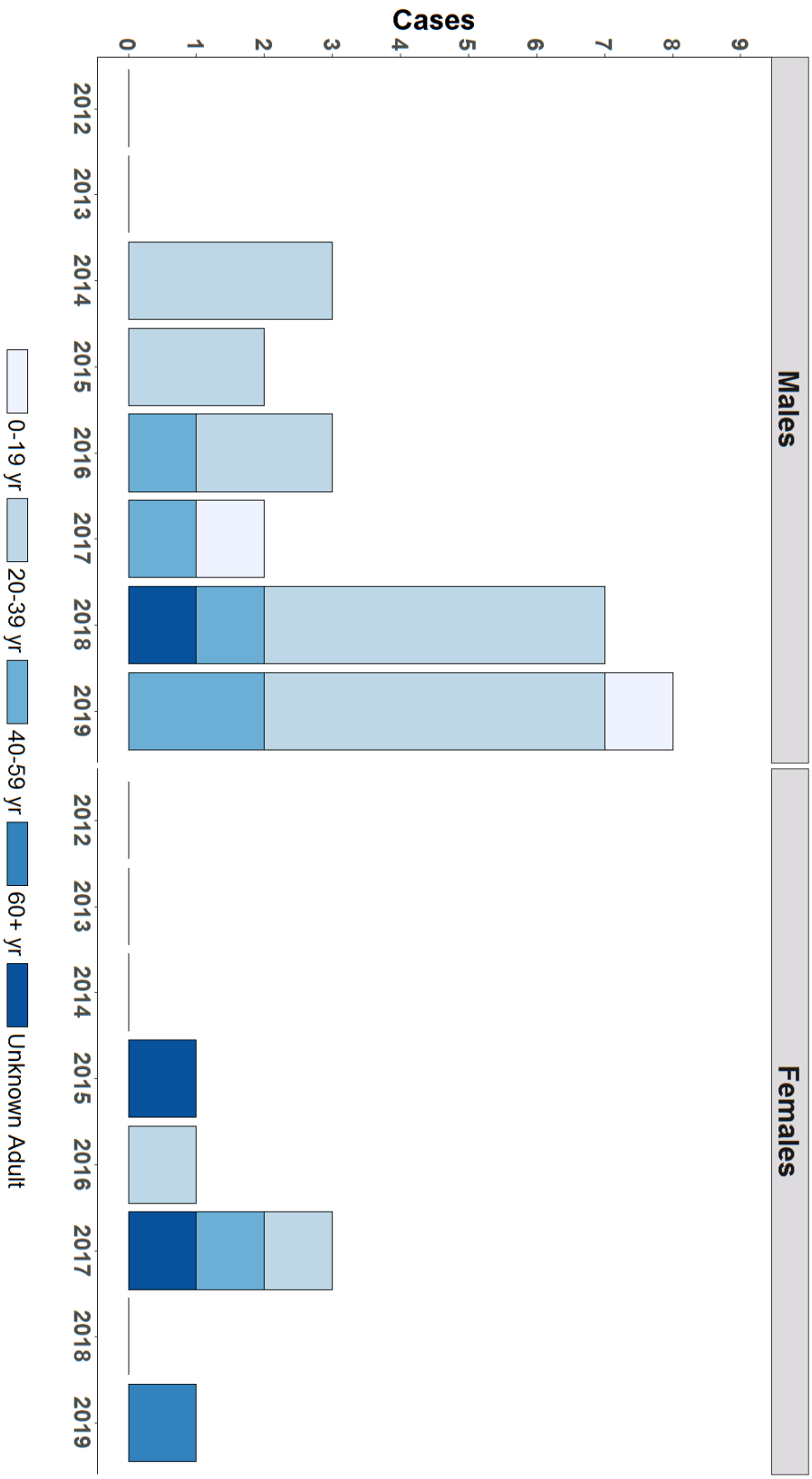

Figure 1: *Kratom exposures managed by the British Columbia Drug and Poison Information Centre, by sex, age and year, 2012-2019*

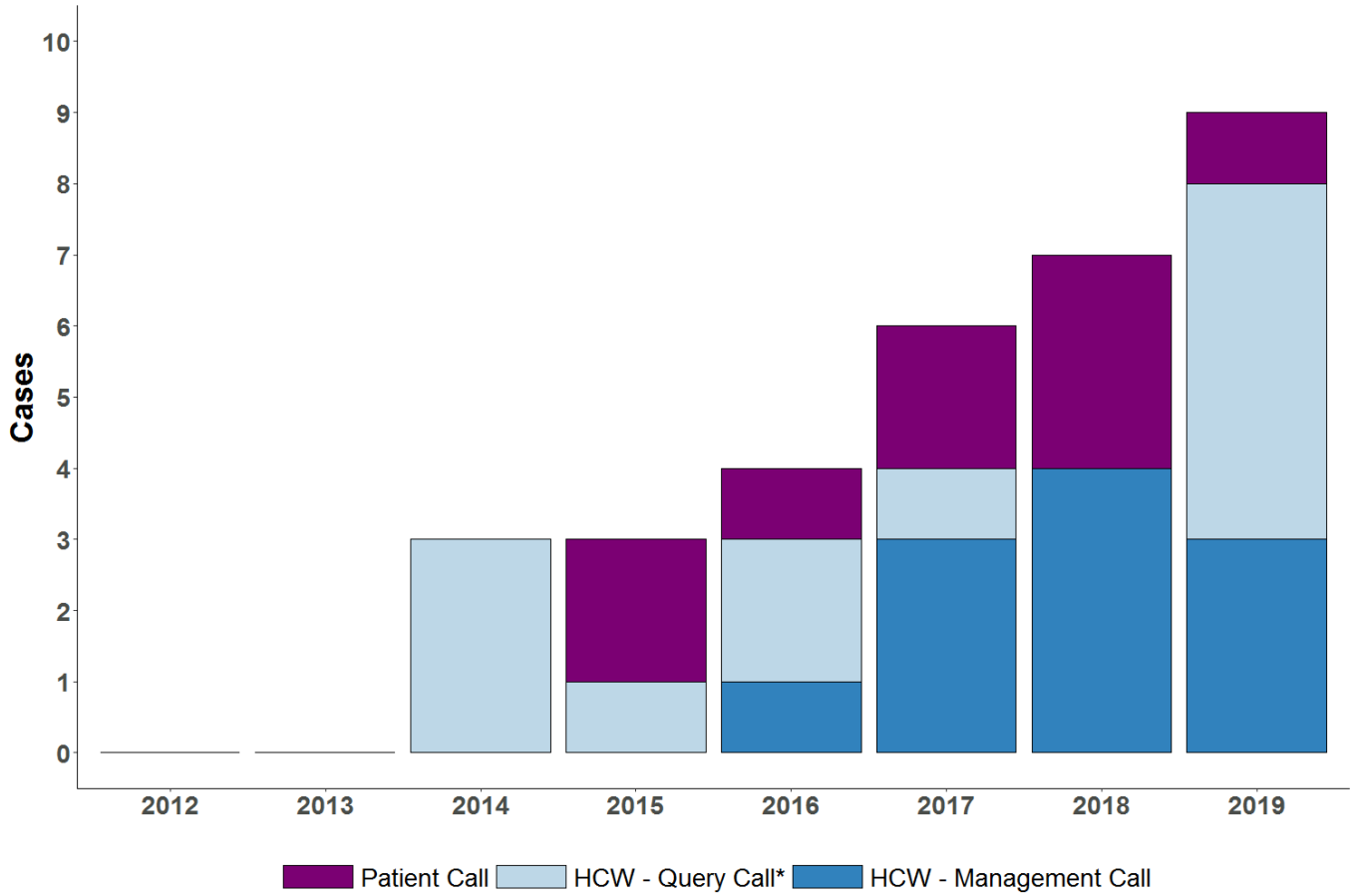

***Figure 2**: Kratom exposure calls by patients (including family and friends) and by health care workers (HCW) and reasons for call from HCW, 2012-2019 (* Query calls about toxicology, drug interactions, etc)*

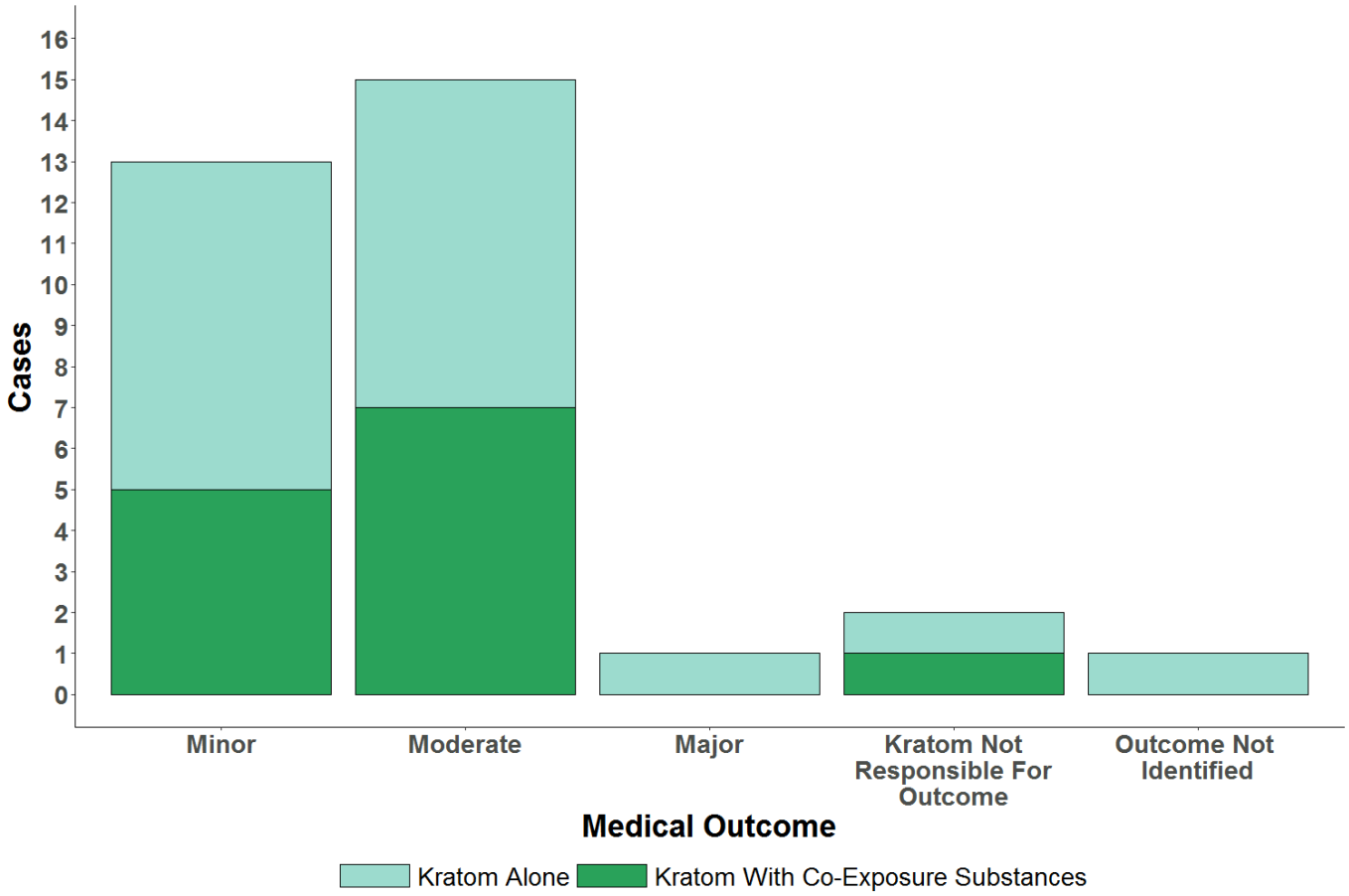

Figure 3: *Medical outcome (based on the National Poison Data System standards) for kratom exposures alone and with co-exposure substances*

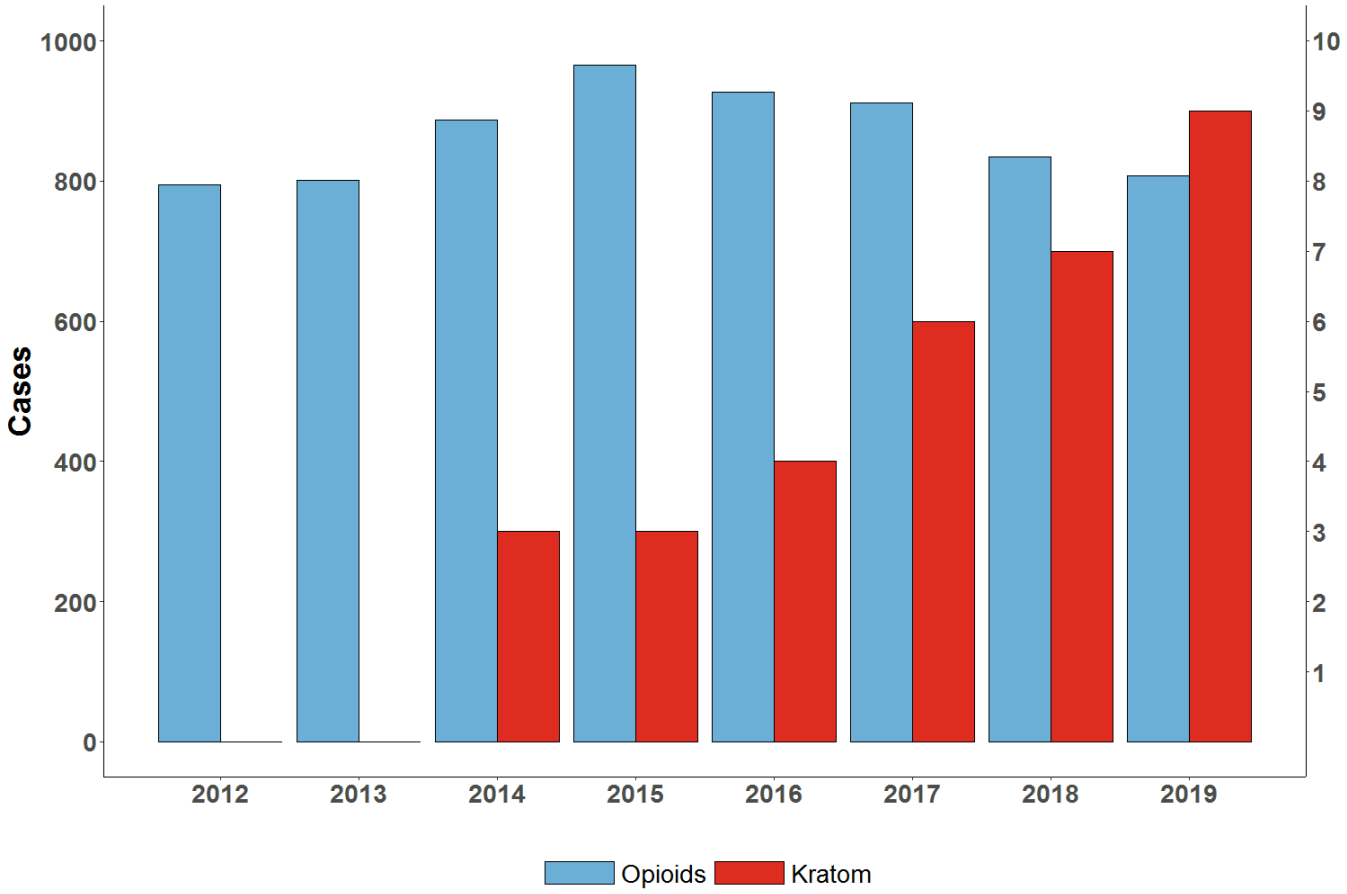

***Figure 4**: Cases managed by the British Columbia Drug and Poison Information Centre for exposure to opioids and to kratom by year, 2012-2019*

Figure Legends

Figure 1: *Kratom exposures managed by the British Columbia Drug and Poison Information Centre, by sex, age and year, 2012-2019*

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Figure 4*: Cases managed by the British Columbia Drug and Poison Information Centre for exposure to opioids and to kratom by year, 2012-2019*

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