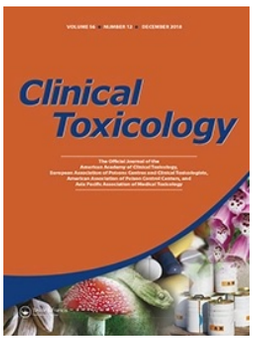

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POISON CENTRE RESEARCH

Acute cannabis toxicity

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ABSTRACT

Objective: We describe the clinical effects of, and products associated with, acute exposures to cannabis during the early legalization period of recreational cannabis in Oregon and Alaska.

Methods: This was an observational study of Oregon/Alaska Poison Center data between 4 December 2015 and 15 April 2017. A standardized data collection instrument was created for this study that captured information about cannabis product description, route of exposure, intentional vs unintentional exposure, product dose, product manufacture source, product ownership source, initial vital signs, clinical signs and symptoms, and subject disposition. Subjects were included if the Poison Center received a call about an acute exposure to cannabis from the subject, subject's family member or friend, or healthcare worker participating in the subject's care. Subjects were excluded if there was no evident exposure, the exposure was chronic, there were co-ingestants, or the subject was non-human (e.g. pet).

Results: Two hundred fifty three individuals were acutely exposed to cannabis (median age 20 years; range 8 months – 96 years; 54.2% males): 71 (28.1%) children (<12 years), 42 (16.6%) adolescents (12–17 years), and 140 (55.3%) adults (≥18 years).

Children were most likely to unintentionally (98.6%) ingest (97.2%) homemade (35.2%) edibles (64.8%) belonging to a family member (73.2%) and experience sedation (52.1%). Adults were most likely to intentionally (88.6%) ingest (66.4%) retail (40.0%) edibles (48.6%) and experience neuroexcitation (47.1%). Adolescents' exposures had similarities to both adult and children; they were most likely to intentionally (81.0%) ingest (50.0%) homemade (23.8%) edibles (45.2%) belonging to a friend (47.3%) and to experience either neuroexcitation (42.9%) or sedation (40.5%).

Among all ages, tachycardia and neuroexcitation were more likely following inhalation exposures compared to ingestions. Eight subjects were admitted to an intensive care unit, including three patients who were intubated; one subject died. Edibles were the most common products to cause symptoms in all age groups, while concentrated products were more likely to lead to intubation, especially when ingested. Children in particular had a higher likelihood of intensive care unit admission and intubation following exposure to concentrated products.

Conclusions: Neurotoxicity is common after acute cannabis exposures. Children experienced unintentional exposures, particularly within the home and occasionally with major adverse outcomes. Concentrated products such as resins and liquid concentrates were associated with greater toxicity than other cannabis products. These findings may help guide other states during the early retail cannabis legalization period.

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Introduction

The cannabis plants (*Cannabis sativa* and *C. indica*) contain over 60 unique cannabinoids, including tetrahydrocannabinol (THC) and cannabidiol (CBD), and have a variety of known clinical effects [1]. As of 1 February 2018, nine of the 50 United States (U.S.) (Colorado, Washington, Alaska, Oregon, California, Maine, Massachusetts, Nevada, and Vermont) and the District of Columbia had approved legalization of recreational ("retail") cannabis, and six U.S. states (Colorado, Washington, Alaska, Oregon, California, and Nevada, listed in chronological order) had operational recreational cannabis retailers.

In November 2014, Alaskan and Oregon voters passed Measures 2 and 91, respectively, legalizing non-medical cannabis for individuals ≥21 years. Recreational cannabis was initially sold from existing medicinal dispensaries, before retailers opened in both states in October 2016. Retail edible cannabis products have been limited in both states to a single serving size of 5 mg THC and a total package limit of 50mg THC (10 servings). Retail concentrate products are limited to 1000mg THC per package in Oregon and 7000mg THC per transaction in Alaska (typically packaged in 500–1000mg quantities). In Oregon, medicinal products may contain up to 100mg THC per package in edibles and 4000mg THC in concentrates; Alaska does not allow medicinal cannabis in edible or concentrated form.

Legalization of cannabis may increase the availability of potent botanical material, extracts, oils, resins, and

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e-cigarette/vaping liquids, as well as edibles that may be attractive to children (e.g. brownies, gummies, cookies) [2–7]. Initial data from states with legalized cannabis suggest increased exposures in children [4,5,7]. Studies of acute clinical effects of cannabis and cannabis components have included case reports and small case series [7–15]. Other studies [16,17] evaluated the U.S. National Poison Data System (NPDS) and reported symptoms after exposures to cannabis products; however detailed data on product and exposure history are not available with NPDS data. We add to the literature by including detailed information about clinical symptoms, product type, THC dose, and product source from acute single-agent cannabis exposures in two of the first U.S. states with operational retail cannabis dispensaries. These data are particularly important in states where recreational/retail cannabis has been legalized as there are a wide variety of edible products, concentrated products, and higher-THC botanical cannabis that are now available and have not been studied.

Methods

This is an observational study of clinical effects following acute cannabis exposures, as reported to the Oregon/Alaska Poison Center (OPC) between 4 December 2015 and 15 April 2017.

OPC receives phone calls from the public, physicians, nurses, paramedics, and other healthcare providers throughout Oregon and Alaska; all calls to a poison center within both states are routed to OPC. On receipt of a call, a Specialist in Poison Information (SPI) provides clinical advice and records demographic information, patient history, vital signs, laboratory evaluation, interventions, and outcomes into a medical chart (ToxiCALL software, version 4.7.37, Computer Automated Systems Inc.). A board-certified physician medical toxicologist is available for consultation on any case 24 h per day.

A standardized data collection instrument was created prior to study commencement, included in the poison center medical record, and used throughout the study. This instrument is available online in a Supplemental Table. At the study's inception, OPC SPIs were informed of its objectives and data collection methodology. The SPIs were instructed to complete data collection for any call relating to a potential cannabis exposure. SPIs were also instructed to inform callers of the study and solicit contact information for the subject or subject's family members if they consented to a follow-up call from a medical toxicologist, which was intended to collect any additional product information not available at the time of initial contact with the poison center. SPIs were instructed to immediately contact the on-call medical toxicologist for each case of potential cannabis exposure, regardless of symptoms, and all of the center's toxicologists were instructed to offer to speak to the caller in order to help collect information for the data collection instrument. SPIs also flagged cases for further review by study authors. Study authors called consenting subjects 1–7 d later and entered any additional product information into the poison center medical record.

At the end of the study period, poison center medical records were queried for all exposures to "marijuana," "cannabis," "THC," "DAB," "hash oil," "butane hash oil," or "BHO" in the substance data field (terms used by SPIs in codifying calls) during the study period.

One study author (MN) reviewed each case, abstracting all data from the data collection instrument plus data that was present in the standard medical record, including subject age, gender, clinical symptoms, treatments administered, call origin, and patient disposition. Data are described using descriptive statistics. Pearson Chi Square was used to test for association of dichotomous outcomes and Fisher's exact test was used when the frequency of events were low (<5 in any data field). Relative risk was calculated to quantify the risk of outcomes. This study was approved by the Oregon Health and Science University Institutional Review Board.

A subject was defined as any individual exposed to a cannabis-containing product about whom OPC received a call during the study period. Exclusion criteria were subjects that did not have an exposure to cannabis (e.g. informational calls), the cannabis exposure was chronic (e.g. cannabinoid hyperemesis syndrome), and subjects that were non-human (e.g. pets). Subjects were also excluded if they were co-exposed to any non-cannabis substances by history (including ethanol, illicit drugs, and nicotine products), but were included if they were exposed only to cannabis simultaneously in multiple forms.

Concentrated cannabis products were divided into cannabis "concentrates" (typically a liquid product whereby cannabis is concentrated by a mechanical process, carbon dioxide, or water or oil solvent, such as glycerin or isopropyl alcohol) or "resins" (typically a solid or semi-solid product whereby cannabis is extracted using high heat and pressure or a hydrocarbon solvent, such as butane). When the production method was not evident, concentrated products were classified as "concentrates" if they were liquid, oil, or intended for vaping, or as "resins" if they were solid or semi-solid. "Butane hash oil (BHO)" was commonly used to describe either resins or concentrates, so "BHO" was classified as a resin if it was solid or semi-solid and as a concentrate if it was intended to be used in an electronic vaporizer or ingested as an oil (e.g. in a dropper). Concentrates and resins were not defined as edibles unless they were combined into an edible food item (e.g. brownies, cookies, etc). The manufacturing source of the product was classified when possible as either retailer/dispensary (i.e. recreational/medicinal) or homemade/homegrown. Adults were defined as $\geq$18 years, as this is the age at which medical cannabis products may be purchased and used. Modified age categories ($<$12 years and 12–20 years) were used to analyze where young adults who cannot legally purchase recreational cannabis ($<$21 years) obtained the product (i.e. "source"). Source of the cannabis was defined as the person to whom the cannabis product belonged or from whom it was obtained, including family member or caretaker, friend or acquaintance, or another specified person. Categories of heart rate and blood pressure values were defined according to published guidelines (available online as a Supplemental Table).

Results

The Oregon/Alaska Poison Center received 68,433 total calls during the study period. 383 (0.6%) OPC charts were identified and reviewed; 253 (66.1%) cases were included (Figure 1). All identified charts used the data collection instrument. Subjects' ages ranged from 8 months to 96 years. Of the 240 (94.9%) subjects with quantitative age data available, the median age was 20 years and the mean age was 25.5 years. Males comprised the slight majority of subjects overall (137, 54.2%) and across all age categories: 41 (57.7%) children, 23 (54.8%) adolescents, and 73 (52.1%) adults.

Most calls originated from an emergency department (ED) (138, 54.5%) or home (95, 37.5%). Less commonly, calls originated from pre-hospital Emergency Medical Services providers (15, 5.9%), a hospital inpatient setting (3, 1.2%), an outpatient healthcare provider (1, 0.4%), and a police welfare check (1, 0.4%). Subject consent for a follow-up call by a medical toxicologist was obtained in only 3.2% (8/253) of cases.

Product dose was reported in 137 (54.2%) exposures, including 36 (14.2%) quantitative and 101 (39.9%) non-quantitative doses (e.g. "one bite"). Quantitative THC doses ranged from 2mg to 1000mg. Most subjects were exposed to 15–50mg THC in edible products, and all hospital admissions occurred after ingestion of $\geq$15mg THC.

Acute cannabis exposures by age

Of the 71 exposures in children, 64 (90.1%) involved at least one of the following factors to support an exposure: witnessed ingestion (48, 67.6%), positive urine drug screening immunoassay result (17, 23.9%), or subject admitted to the ingestion (15, 21.1%). Almost all (41/42; 97.6%) exposed adolescents either admitted to the exposure (40/42, 95.2%) and/or had a positive urine drug screening immunoassay (6, 14.3%). Almost all adult exposures (136/140; 97.1%) were self-proclaimed or witnessed.

Edible products represented the most common exposures across all ages, including the majority of children (Table 1). More ingestion exposures were reported than all other routes combined across all age groups. Adolescents had significantly higher percentage of inhalational exposures than adults. Almost all exposures in children were accidental, while the majority of adolescent and adult exposures were intentional.

Adult exposures were more likely to involve cannabis purchased from a retailer/dispensary, whereas adolescents and children were more likely to be exposed to homemade/homegrown cannabis products (Table 1). Of the 9 concentrated product exposures in children, almost half (4, 44.4%) were homemade/homegrown. Most children were exposed to cannabis products belonging to a family member or caretaker, including 34 (91.9%) of 37 subjects $\leq$2 years. There were 55 exposures in underage adults (ages 12–20): the cannabis involved in these exposures most commonly belonged to a friend (Table 1), and was homemade/homegrown (11/55, 20.0%), commercially-produced (11/55, 20.0%), or from an unknown/unspecified source (33/55, 60.0%).

Vital sign data are presented in Table 1. Heart rate, blood pressure, and oxygen saturation were only reported in 55.3%, 32.4%, and 21.7% of cases, respectively, so analysis is limited. Vital sign data were unavailable in 22.9% of cases because the patient was never evaluated in a health care facility (Table 1). Of those that had vital sign data reported, more children had a normal heart rate compared to tachycardia, while the opposite was true for adolescents and adults.

Any adverse clinical effects were reported in 227 (89.7%) subjects (Table 2). Neurotoxicity was reported in the majority of subjects overall and within each age group. Central nervous system (CNS) depression was more common in children, whereas CNS excitation was more common in adults. Adolescents experienced roughly equivalent incidence of CNS depression and CNS excitation. Anxiety, paranoia, or panic attack were reported in nearly one in three adults, and lightheadedness/dizziness/vertigo was reported in nearly one in five adults.

The majority of patients received no treatment, including 50 (70.4%) children, 25 (59.5%) adolescents, and 81 (57.9%) adults. Twenty-one (15.0%) adults and 4 (9.5%) adolescents

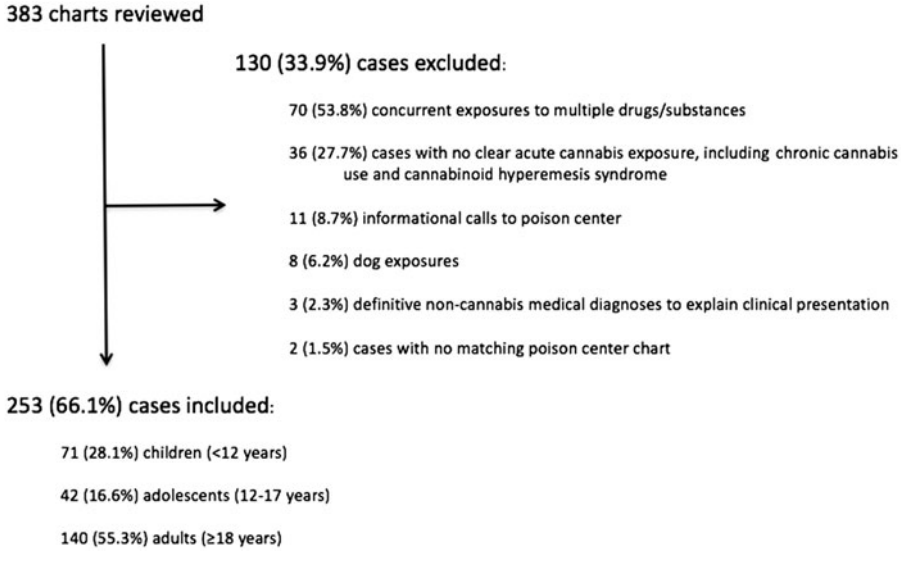

Figure 1. Included and excluded cases, by age category of included subjects and reasons for exclusion.

Table 1. Exposure details and clinical effects of cannabis exposures by age category.

	Children (<12 years) ($n = 71$)	Adolescents (12–17 years) ($n = 42$)	Adults (≥18 years) ($n = 140$)	Total ($N = 253$)
Product type				
Edible	48 (67.6%)	20 (47.6%)	76 (54.3%)	144 (56.9%)
Botanical	11 (15.5%)	9 (21.4%)	22 (16.3%)	42 (16.6%)
Concentrated products:	9 (12.6%) *	12 (28.6%)	36 (25.7%)	57 (22.5%)
Concentrate	6 (8.4%)	1 (2.4%) *	24 (17.1%)	31 (12.2%)
Resin	3 (4.2%)	11 (26.2%) **	12 (8.6%)	26 (10.3%)
Unknown	3 (4.2%)	1 (2.1%)	6 (4.3%)	10 (4.0%)
Route of exposure				
Ingestion	69 (97.2%) **	22 (52.3%) *	96 (68.6%)	187 (73.9%)
of edible	48 (67.6%)	20 (47.6%)	76 (54.3%)	144 (56.9%)
of botanical	11 (15.5%) **	0 (0%)	1 (0.7%)	12 (4.7%)
of concentrate	5 (7.0%)	1 (2.4%)	16 (11.4%)	22 (8.7%)
of resin	3 (4.2%)	1 (2.4%)	3 (2.1%)	7 (2.8%)
of unknown	2 (2.8%)	0 (0%)	0 (0%)	2 (0.8%)
Inhalation	1 (1.4%) **	19 (45.2%) *	37 (26.4%)	57 (22.5%)
of botanical	0 (0%) **	9 (21.4%)	21 (15.0%)	30 (11.9%)
of concentrate	1 (1.4%)	0 (0%)	7 (5.0%)	8 (31.6%)
of resin	0 (0%) *	10 (23.8%) **	9 (6.4%)	19 (7.5%)
Topical/parenteral/rectal	0 (0%)	0 (0%)	2 (1.4%)	2 (0.8%)
Unknown/other	1 (1.4%)	1 (2.4%)	5 (4.5%)	7 (2.8%)
Intent of exposure				
Intentional	0 (0%) **	34 (81.0%)	124 (88.6%)	158 (62.5%)
Unintentional	70 (98.6%) **	7 (16.7%) *	15 (10.7%)	92 (36.4%)
Unknown	1 (1.4%)	1 (2.4%)	1 (0.7%)	3 (1.2%)
Manufacturing source				
Homemade/grown	25 (35.2%) **	10 (23.8%)	24 (17.1%)	59 (23.3%)
Retailer/dispensary	17 (23.9%) *	7 (16.7%) **	56 (40.0%)	80 (31.6%)
Unknown/unspecified	29 (40.8%)	25 (60.0%)	60 (42.9%)	114 (45.1%)
Vital signs				
Heart Rate				
Normal	20 (28.2%)	7 (16.7%)	29 (20.7%)	56 (22.1%)
Tachycardia	13 (18.3%) *	18 (42.9%)	46 (32.9%)	77 (30.4%)
Bradycardia	2 (2.8%)	2 (4.8%)	3 (2.1%)	7 (2.8%)
Unknown	36 (50.7%)	15 (35.7%)	62 (44.3%)	113 (44.7%)
Blood pressure				
Normal	11 (15.5%)	4 (9.5%)	33 (23.6%)	48 (19.0%)
Hypertension	6 (8.5%)	8 (19.0%)	13 (9.3%)	27 (10.7%)
Hypotension	2 (2.8%)	2 (4.8%)	3 (2.1%)	7 (2.8%)
Unknown	52 (73.2%)	28 (66.7%)	91 (65.0%)	171 (67.6%)
Oxygen saturation				
Normal	19 (26.8%)	4 (9.5%)	29 (20.7%)	52 (20.6%)
Hypoxemia	1 (1.4%)	0 (0%)	2 (1.4%)	3 (1.2%)
Unknown	51 (71.8%)	38 (90.5%)	109 (77.9%)	198 (78.3%)
Disposition				
ICU	4 (5.6%)	1 (2.4%)	3 (2.1%)	8 (3.2%)
Ward admission	14 (19.7%) **	2 (4.8%)	6 (4.3%)	22 (8.7%)
ED, then discharged	34 (47.9%)	26 (61.9%)	81 (57.9%)	141 (55.7%)
Kept at home	10 (14.1%) *	9 (21.4%)	39 (27.9%)	58 (22.9%)
Died	0 (0%)	0 (0%)	1 (0.7%)	1 (0.4%)
Product ownership source	**Children (<12 years)**	**Adolescents and underage adults (12–20 years) ($N = 55$)**		**Total (%) ($N = 126$)**
Family member or caretaker	52 (73.2%) **	4 (7.3%)		56 (44.4%)
Friend	6 (8.5%) **	26 (47.3%)		32 (25.4%)
Other specified individual	7 (9.9%)	1 (1.8%)		8 (6.3%)
Unknown or unspecified	6 (8.5%) **	24 (43.6%)		30 (23.8%)

*,**Compared to adults, using Chi Square or Fischer's exact (if cell value <5); *$p < .05$; **$p < .01$.

received benzodiazepines; 14 (10.0%) adults and 5 (11.9%) adolescents received anti-emetics. Three subjects including 2 infants were intubated: 1 infant and 1 adult ingested a liquid concentrate and 1 infant ingested a semi-solid resin (BHO) (Table 3). All developed severe CNS sedation and respiratory depression, with 1 infant developing respiratory failure. All 3 subjects were successfully extubated the following day without apparent sequelae.

Acute cannabis exposures by product

Twelve subjects ingested botanical products (e.g. leaves or buds) (Table 4), 11 (91.7%) of whom were 4 years old or younger. Those with symptoms developed CNS depression more commonly than excitation. One 12-month-old infant ingested a bud of 26% THC cannabis and developed neuroexcitation, irritability, and had a positive urine immunoassay for THC.

Subjects who inhaled cannabis (in all forms) were generally adolescents and adults and most commonly developed CNS excitation (27/57, 47.4%) and tachycardia (26/57, 45.6%); most were cared for in the emergency department and discharged (38/57, 66.7%) (Table 4). Among all-ages single-route exposures with known heart rate ($N = 133$), tachycardia was more likely following inhalation exposure compared to all other exposures (RR 1.58; 95%CI 1.20–2.08, $p = .0012$). Of the

Table 2. Detailed clinical effects following acute cannabis exposure by age category, including organ system and central nervous system (CNS) subcategories.

	Children	Adolescents	Adults	Total
Neurologic (any, total)	**49 (69.0%)** **	**36 (85.7%)**	**119 (85.0%)**	**204 (80.6%)**
CNS excitation (any, total):	**13 (18.3%)** **	**18 (42.9%)**	**66 (47.1%)**	**97 (38.3%)**
Anxiety, paranoia, panic attack	** 1 (1.4%)	8 (19.0%)	46 (32.9%)	55 (21.7%)
Hallucinations, visual disturbances	1 (1.4%)	4 (9.5%)	7 (5.0%)	12 (4.7%)
Agitated, irritable, aggressivea	7 (9.9%)	5 (11.9%)	10 (7.1%)	22 (8.7%)
Psychosis	0 (0%)	0 (0%)	4 (2.9%)	4 (1.6%)
Seizure	3 (4.2%)	2 (4.8%)	4 (2.9%)	9 (3.6%)
Tremors, myoclonusb	2 (2.8%)	2 (4.8%)	4 (2.9%)	8 (3.2%)
CNS depression (any, total):	**37 (52.1%)** **	**17 (40.5%)** *	**33 (23.6%)**	**87 (24.4%)**
Reduced consciousnessc	** 32 (45.1%)	** 14 (33.3%)	11 (7.9%)	57 (22.5%)
Obtunded, comatose, unresponsive	* 4 (5.6%)	1 (2.4%)	1 (0.7%)	6 (2.4%)
Syncope, fall, found down	2 (2.8%)	4 (9.5%)	5 (3.6%)	11 (4.3%)
Confusion	0 (0%)	1 (2.4%)	4 (2.9%)	5 (2.0%)
Speech abnormalities	0 (0%)	3 (7.1%)	3 (2.1%)	6 (2.4%)
Weakness, impaired coordination	2 (2.8%)	2 (4.8%)	14 (10.0%)	18 (7.1%)
Other neurotoxicity (any, total):	**13 (18.3%)** **	**13 (31.0%)**	**57 (40.7%)**	**83 (32.8%)**
Altered (otherwise unspecified)d	9 (12.7%)	4 (9.5%)	12 (8.6%)	25 (9.9%)
Dysphoriae	* 0 (0%)	1 (2.4%)	9 (6.4%)	10 (4.0%)
Euphoria	2 (2.8%)	0 (0%)	1 (0.7%)	3 (1.2%)
Unusual/unexpected subjective sensationf	1 (1.4%)	2 (4.8%)	6 (4.3%)	9 (3.6%)
Numbness, tingling	0 (0%)	0 (0%)	6 (4.3%)	6 (2.4%)
Headache	0 (0%)	0 (0%)	3 (2.1%)	3 (1.2%)
Lightheadedness, dizziness, vertigo	** 2 (2.8%)	8 (19.0%)	26 (18.6%)	36 (14.2%)
Cardiac (any, total)	**1 (1.4%)** **	**5 (11.9%)**	**31 (22.1%)**	**37 (14.6%)**
Palpitations	** 0 (0%)	3 (7.1%)	25 (17.9%)	28 (11.1%)
Chest pain/discomfort	1 (1.4%)	2 (4.8%)	8 (5.7%)	11 (4.3%)
Gastrointestinal (any, total)	**7 (9.9%)** **	**17 (40.5%)**	**43 (30.7%)**	**67 (26.5%)**
Nausea without vomiting	* 0 (0%)	5 (11.9%)	10 (7.1%)	15 (5.9%)
Vomiting without nausea	7 (9.9%)	4 (9.5%)	13 (9.3%)	24 (9.5%)
Nausea and vomiting	** 0 (0%)	6 (14.3%)	18 (12.9%)	24 (9.5%)
Abdominal pain or cramping	0 (0%)	3 (7.1%)	3 (2.1%)	6 (2.4%)
Diarrhea	0 (0%)	0 (0%)	2 (1.4%)	2 (0.8%)
Respiratory (any, total)	**2 (2.8%)**	**2 (4.8%)**	**5 (3.6%)**	**9 (3.6%)**
Respiratory depression	2 (2.8%)	0 (0%)	1 (0.7%)	3 (1.2%)
Dyspnea	0 (0%)	1 (2.4%)	3 (2.1%)	4 (1.6%)
Cough	0 (0%)	1 (2.4%)	1 (0.7%)	2 (0.8%)
Hyperthermia	**1 (1.4%)**	**0 (0%)**	**0 (0%)**	**1 (0.4%)**
Explicitly asymptomatic	**11 (15.5%)** **	**2 (4.8%)**	**3 (2.1%)**	**16 (6.3%)**

Subjects may have had multiple symptoms within any organ system or subcategory, such as palpitations and chest discomfort, or anxiety and tremors. Therefore, values within age groups may sum to greater than 100% (e.g. neurotoxicity subcategories of adolescents), and numbers of subjects with any specific symptom within an organ system may sum to greater than the total number of subjects for that system (e.g. subject with both vomiting and abdominal pain).

[a]including "inconsolable," "restless," "hyperactive," "distressed," "labile," "pressured," "fidgety," "combative".

[b]including "shaky," "rigid".

[c]including "sleepy," "drowsy," "somnolent," "lethargic," "stoned," "tired," "spacey," "out of it," "dazed".

[d]including "impaired," "intoxicated," "strange," "high," "trippy," "disoriented".

[e]including "sick," "awful," "terrible," "anhedonia," "too high," "miserable," "scared".

[f]including "out of body," "feels funny," "strange," "weird," "goofy," "bizarre".

*,**Compared to adults, using Chi Square or Fischer's exact (if cell value <5); *$p < .05$; **$p < .01$.

219 all-ages single-route inhalation or ingestion exposures with either CNS excitation or depression, subjects were more likely to develop CNS excitation after inhalation than after ingestion (RR 1.54, 95%CI 1.04–2.27, $p < .03$). Similarly, of the 241 all-ages single-route inhalation or ingestion exposures with any CNS effect, CNS excitation without depression was also more likely than all other non-excitation CNS effects after inhalation than after ingestion (RR 1.51, 95%CI 1.01–2.25, $p < .05$).

One hundred forty four subjects ingested edibles, with similar rates of CNS excitation (47/144, 32.6%) or CNS sedation (46/144, 31.9%), and when heart rate was recorded, they had generally equivalent rates of normal heart rate (38/82, 46.3%) or tachycardia (42/82, 51.2%) (Table 4). There were 68 edible exposures in children and adolescents (Table 1): most of these cases resulted in emergency department visits, with 9% being admitted to a hospital ward, and 2% admitted to an intensive care unit (ICU).

Subjects exposed to resins developed both CNS excitation (10/26, 38.5%) and sedation (9/26, 34.6%) and when heart rate was recorded, more tachycardia (8/14, 57.1%) than normal heart rate (4/14, 28.6%) or bradycardia (2/14, 14.3%) (Table 4). Compared to ingestion, inhalation of resins appeared to have higher rates of CNS excitation and tachycardia (Table 4). One 12-month-old infant ingested semi-solid BHO and developed tachycardia, seizures, obtundation, and respiratory failure and was intubated (Table 3).

Subjects with liquid concentrate exposures developed slightly more CNS excitation (10/30, 33.3%) than sedation (8/30, 26.7%), and tachycardia was common after inhalational liquid concentrate exposures (Table 4). One 9-month-old infant ingested a commercial liquid concentrate and developed respiratory depression and was intubated (Table 3). One 55-year-old man ingested a commercial liquid concentrate and developed tachycardia and obtundation and was intubated (Table 3). One 70-year-old man died shortly after presentation to the ED after intentional inhalational exposure

Table 3. Demographic, exposure, and clinical details for all 8 subjects admitted to an intensive care unit.

Age	Gender	Intentional/ unintentional	Route	Product	Amount	Ownership	Clinical effects	Treatment
9 months	M	unintentional	ingestion	concentrate (commercial)	unknown	parents	syncope, fall, somnolence, respiratory depression	intubation and ventilation, aeromedical transfer to tertiary care center
1 year	M	unintentional	ingestion	butane hash oil (homemade)	unknown	parents	tachycardia, agitation, witnessed seizures, obtundation, respiratory failure	intubation and ventilation, aeromedical transfer to tertiary care center
2 years	F	unintentional	ingestion	cookie (homemade)	1 cookie	parents	tachycardia, hypertension, lethargy	none
4 years	F	unintentional	ingestion	chocolate bar (commercial)	30 mg THC	family member	tachycardia, somnolence	intravenous fluids
teenage	M	intentional	inhalation	concentrate (unknown)	unknown	unknown	agitation	ketamine
33 years	M	intentional	inhalation	botanical material (unknown)	unknown	unknown	seizure	none
55 years	M	unintentional	ingestion	dessert bar (homemade)	1 bar	friend	tachycardia, myoclonic jerking, unwanted subjective sensation	none
55 years	F	intentional	ingestion	liquid concentrate (commerical)	4 drops	self	tachycardia, obtundation	intubation and ventilation, bicarbonate infusion

Table 4. Detailed clinical effects following acute cannabis exposure by product type and route of exposure, including organ system and central nervous system (CNS) subcategories.

	Botanical cannabis		Edible			Resin		Liquid concentrate	
	Ingestion	Inhalation	Ingestion Homemade[a]	Ingestion Commercial[b]	Ingestion Unknown source[c]	Ingestion[d]	Inhalation[e]	Ingestion[f]	Inhalation[g]
	$n = 12$	$n = 30$	$n = 48$	$n = 60$	$n = 36$	$n = 7$	$n = 19$	$n = 22$	$n = 8$
Age (median)	21mo	26yr	15yr	22yr	20yr	15yr	18yr	43yr	20yr
Age (range)	8mo–43yr	14yr–64yr	16mo–67yr	17mo–96yr	14mo–80yr	9mo–57yr	13yr–34yr	17mo–76yr	18mo–70yr
Male (n,%)	10 (83%)	18 (60%)	20 (43%)	30 (50%)	16 (44%)	5 (71%)	14 (74%)	9 (41%)	7 (88%)
Primary presenting symptom:									
Neurologic[h]:									
CNS excitation (n,%):	2 (17%) *	15 (50%)	14 (29%)	21 (35%)	12 (33%)	2 (29%)	8 (42%)	6 (27%)	4 (50%)
CNS depression (n,%):	4 (33%)	4 (13%)	15 (31%)	18 (30%)	13 (36%) *	3 (43%)	6 (23%)	7 (32%)	1 (13%)
Altered mental status (n,%):	0	5 (17%)	7 (15%)	10 (17%)	10 (28%)	0	2 (11%)	5 (23%)	0
Gastrointestinal, nausea or vomiting (n,%):	1 (8%)	3 (10%)	2 (4%)	3 (5%)	0	0	2 (11%)	1 (5%)	0
Other symptoms (n,%):	1 (8%)	3 (10%)	4 (8%)	7 (12%)	0	1 (14%)	1 (5%)	0	2 (25%)
Respiratory depression with intubation (n,%):	0	0	0	0	0	1 (14%)	0	2 (9%) **	0
Asymptomatic (n,%):	4 (33%) **	0	6 (13%)	1 (2%)	1 (3%)	1 (14%)	0	3 (14%)	1 (13%)
Heart rate[h]:									
Tachycardia (n,%):	2 (17%) *	15 (50%)	16 (33%)	15 (25%)	11 (31%)	1 (14%)	7 (37%)	4 (18%) *	4 (50%)
Normal heart rate (n,%)	2 (17%)	3 (10%)	13 (27%)	15 (25%)	10 (28%)	1 (14%)	3 (16%)	5 (23%)	1 (13%)
Bradycardia (n,%)	1 (8%)	1 (3%)	1 (2%)	1 (2%)	0	2 (29%)	0	0	0
Disposition:									
Home	6 (50%)	9 (30%)	6 (13%) *	15 (25%)	8 (22%)	1 (14%)	3 (16%)	8 (36%)	2 (25%)
ED visit	2 (17%) *	19 (63%)	37 (77%)	31 (52%)	21 (58%)	4 (57%)	14 (74%)	9 (41%)	5 (63%)
Hospital ward admission	4 (33%) *	1 (3%)	3 (6%)	6 (10%)	4 (11%)	1 (14%)	1 (5%)	3 (14%)	0
ICU admission	0	1 (3%)	2 (4%)	1 (2%)	0	1 (14%)	1 (5%)	2 (9%)	0 (1 died)

*,**Compared to botanical inhalation, using Chi Square or Fischer's exact (if cell value <5); *$p < .05$; **$p < .01$.

[a]Homemade edible: 38% brownie; 25% cookie; 19% cake/cupcake; 4% gummy, bread; 2% butter, candy, homemade capsule, zucchini bread, rice crispy bar, oil on popcorn.

[b]Commercial edible: 37% candy; 15% gummy; 12% chocolate; 10% brownie; 7% cookie; 2% cake, trail mix, tea, mints, wafer, "orange slices".

[c]Edible with unknown source: 50% brownie; 25% cookie; 9% chocolate.

[d]Resin ingestion: 72% Dab; 14% "wax", "resin".

[e]Resin inhalation: 95% Dab; 5% resin scraped from a pipe and smoked.

[f]Concentrate ingestion: 50% concentrate vaping liquid or oil; 18% hash oil; 9% Rick Simpson Oil, capsule, topical paste; 5% sublingual spray, wax.

[g]Concentrate inhalation: 45% hash oil; 23% concentrate vaping liquid; 14% capsule; 9% Rick Simpson Oil; 5% paste, sublingual spray.

[h]Numbers are percentages of all patients and may not add to 100% as some were unknown or unreported.

1 patient treated in jail, but not included in "home".

to vaporized liquid concentrate product, with documented wide-complex tachydysrhythmia and ST-segment elevation on electrocardiogram. Autopsy revealed acute myocardial infarction of the anterior left ventricular wall, acute thrombosis of the left anterior descending artery, and atherosclerotic disease of multiple coronary arteries [18].

Among subjects with single-route exposure to a known cannabis product ($N = 238$), subjects who used concentrated cannabis products (liquids, resins, extracts) had a higher incidence of intubation than those who used non-concentrated products (3/29 vs 0/209; $p < .01$). Children who were exposed to a concentrated cannabis product also had a higher incidence of intubation than those exposed to non-concentrated products (2/9 vs 0/62, $p = .01$).

Eight subjects were admitted to an intensive care unit (Table 3). ICU admission was more likely following exposure to concentrated cannabis products than other cannabis products in children (RR 8.29, 95%CI 1.37–49.94, $p = .02$), but not necessarily among all subjects (RR 2.81, 95%CI 0.72–10.92, $p = .14$).

Discussion

This is a 16-month cohort of subjects with acute exposures to cannabis products in the 3rd and 4th U.S. states with operational recreational cannabis retailers. These cases may reflect more severe adverse clinical events, since our data represent interactions with the poison center and asymptomatic subjects may be less likely to encounter healthcare resources.

For all ages, edible products and ingestion were the most common form and route of exposure, respectively. Prior research [6] has suggested that adult ingestion exposures may reflect inadvertent overuse, and this appears consistent with our study, particularly since commercial edible products were relatively new and users may be inexperienced with dosing and/or onset of timing of intended effects. The predominance of edible products in children's exposures may reflect hand-mouth behaviors among toddlers as well as a propensity among school-age children for desserts and candies. Of concern, most children were unintentionally exposed to edible products that belonged to a family member or caretaker. Despite earlier arguments [3,5–7,10–13,19] for protecting against cannabis exposures in children, more attention is still needed to better secure these products in the home.

Neurotoxicity was variable but common following cannabis exposure. Similar to our data, previous smaller studies have noted a high rate of CNS depression in pediatric ingestions, particularly of edible products [13,16,19]. The predominance of CNS depression in children may conceivably represent a greater weight-based dose effect or a physiologically unique response. Greater CNS depression in children may also reflect that children's primary form of exposure was ingestion of edibles, as opposed to inhalation. CNS depression may also be underreported among adults in this study, since sedated adult subjects may be less likely to contact the poison center or present to an ED. The significant predominance of CNS excitation after inhalational use may be explained by the rapid absorption of THC, cannabis's primary psychoactive component [20,21].

Subjects received a variety of treatments, presumably guided by the clinical judgment of treating providers, which may be expected to change according to familiarity with these presentations. Respiratory depression, intubation, and ICU admission were more common after exposures to concentrated cannabis products, particularly in children. Further efforts to limit the harms of these products, including preventing misuse in adults and exposures in children, should be explored.

This study has several limitations. Exposure was established by history and confirmatory testing was not part of the inclusion criteria nor recorded in most cases. However, exposure in children was admitted, witnessed, or supported by positive urine drug screening immunoassay results in almost all cases.

These data represent calls made to the Oregon/Alaska Poison Center, more than half of which originated from emergency departments. The data certainly do not reflect the entire burden of cannabis-related harms in these states and may not be representative of other U.S. states or nations with legalized cannabis. Multiple factors may vary in different locations that might affect the clinical symptoms identified, including cannabis serving size dose, maximum dose allowed in a single package, types of cannabis edible or concentrated products, required packaging and labeling, and child resistant packaging.

Efforts were made to standardize data collection methods, however significant heterogeneity persisted and our data were often incomplete. THC dose information was influenced by recall bias, intentional or unintentional mis-estimation, and often reported in vague amounts such as "one bite," "one brownie [of unknown potency]," or "1–2 hits." Most homemade/homegrown products had unknown or unreliable concentrations. Some patients were unable to provide product or dose information due to alteration of mental status. Vital signs may not have been entered into the data collection instrument unless they were abnormal. Difficulty obtaining complete data has been noted in previous studies of cannabis toxicity as well as studies in illicit drug use [4,14] and may be related to subjects' inability or unwillingness to share complete data involving substances where there may be negative ramifications to the subject. Consent for a follow-up telephone call was obtained in few cases and may have been influenced by subjects' disinterest in further investigation. No follow-up calls revealed any new clinical information and few calls yielded additional reliable product information because subjects had obtained the cannabis from another person or the packaging was lost, discarded, or unavailable. Incomplete subject weight data also limited analysis of weight-based clinical effects and outcomes.

While efforts were made to obtain data prospectively using the data collection instrument, real-time involvement of medical toxicologist, and follow-up calls to subjects, there are nonetheless inherent limitations of a poison center database.

Conclusions

We report cannabis-related acute toxicity in all age groups, which may help guide other states in the early retail cannabis legalization period. Children were most likely to unintentionally ingest homemade edible products belonging to a family member and to experience CNS sedation, a higher risk of ICU admission, and rare respiratory depression prompting intubation especially after exposure to resins and liquid concentrate products. Adolescents were most likely to intentionally ingest homemade edible products belonging to a friend and to experience tachycardia and unpredictable neurotoxicity. Adults were most likely to intentionally ingest retail edible products and to experience tachycardia and CNS excitation. Edibles were the most common product to cause symptoms in all age groups. Inhalational exposures to botanical material, liquid concentrates, and resins were more likely to cause tachycardia and CNS excitation than ingestions. Ingestions of concentrated products resulted in all cases of intubation and most cases of ICU admission.

Disclosure statement

No potential conflict of interest was reported by the authors.

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