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Research Paper

Cannabis and synthetic cannabinoid exposure reported to the Israel poison information center: Examining differences in exposures to medical and recreational compounds

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ABSTRACT

Background: Increasing use of cannabis for medical and recreational purposes has augmented concerns about associated poisoning, and specifically pediatric and adolescent poisonings. Synthetic cannabinoids, often marketed as cannabis replacement, have recently emerged and knowledge and awareness of their toxic effects is growing. The objective of this study was to characterize and compare cannabinoid poisonings (medical and recreational cannabis, and synthetic cannabinoids) in Israel during the period 2007–2018.

Methods: The three types of cannabinoid exposures reported to the Israel Poison Information Center (IPIC) between 2007 and 2018 were identified. Differences in distribution of the three types of agents with respect to demographic and clinical factors were examined using univariate statistics, and time trends were plotted.

Results: Out of the total 615 poison-exposure cases identified, 55% were recreational cannabis cases, 33% were synthetic cannabinoid cases and 12% were medical cannabis cases. Compared to recreational cannabis exposures, synthetic cannabinoid exposures were more likely to be male, to have both gastrointestinal and cardiovascular manifestations and less likely to be called in by the public as opposed to called in by health care professionals and less likely to be treated on-site. Medical cannabis exposures were less likely to be male, more likely to be called in by the public, less likely to present with co-use of other substances and more likely to have gastrointestinal manifestations. Throughout the study period an increase in exposure cases were observed for medical and recreational cannabis cases, whereas synthetic cannabinoid cases showed an increase until 2014 and then a steep decrease.

Conclusions: Despite the low toxicity of different types of cannabinoids, training of physicians and other health care professionals related to cannabinoid poisoning is important. This is particularly important in jurisdictions where legal access to cannabis is becoming increasingly available.

Introduction

Cannabis policies have changed drastically in various places around the globe during the last decades. Israel has been running a Medical Cannabis (MC) program since the early 1990s, and there has been a substantial increase in MC licensed patients over the two last decades; what started out as a small program serving only a few hundred patients, the Israeli MC program is today a comprehensive treatment program serving over 30,000 licensed patients (Zarhin, Negev, Vulfsons & Sznitman, 2018). With the expansion of the MC program, there has also been an increase in availability of high tetrahydrocannabinol (THC) MC products as well as edibles (including tinctures, oils and foods that contain cannabis) which may increase the risk of cannabis poisoning.

While cannabis use for recreational purposes remains illegal in Israel, there has been reports of a substantial increase in recreational cannabis use. A 2017 national survey by Israel's Anti-Drugs and Alcohol National Authority found that 37% of adults had consumed cannabis at least once in the last year. This represents an increase from 9% in 2009 (Harel-Fisch, 2017) and one of the highest rates reported in the world (Isralowitz & Reznik, 2018; UNODC, 2017). Increases in recreational cannabis use have been observed among Israeli adolescents as well,

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although these increases have been smaller (Harel-Fisch, 2017). The increases in cannabis use may signal wide ranging attitude shifts. Indeed, the Israeli government recently approved the "Non-Assault of Liability" bill, which decriminalizes personal use of cannabis for recreational purposes. The law went into effect April 2019.

In addition to increases in the use of plant-based cannabis, the last two decades have seen the introduction of different compounds of synthetic cannabinoids-laced "herbal incense" (e.g. K2, spice, nice guy). Synthetic cannabinoids are designer drugs that are structurally different from plant derived cannabinoids but bind to the same cannabinoid receptors in the human body with a much greater affinity (Brewer & Collins, 2014; Fattore & Fratta, 2011; Wells & Ott, 2011). The substances first appeared in Europe in 2004 and spread across different countries, with an almost ever-increasing synthesis of new derivatives (e.g. JWH, HU, and CP series). According to national surveys conducted by the Israel's Anti-Drugs and Alcohol National Authority, last year prevalence rates of synthetic cannabinoids use were 4.5% among Israeli adults and 3.5% among Israeli adolescents in 2016 (Reiss & Harel-Fish, 2017). No time trend data are available for use of synthetic cannabinoids in Israel. Israel was, however, one of the first countries to create legislation against these new psychoactive synthetic substances with “The Struggle to Combat the Use of Dangerous Substances Law”. The law was enacted in 2013 and provided authorities with new tools to minimize the manufacture and distribution of synthetic cannabinoids (Kahana, 2019).

Compared to other illicit and psychoactive substances, cannabis is regarded as having low acute toxicity. Yet, while most people exposed to cannabis will not experience any detrimental effects (Eisen et al., 2002; Wagner & Anthony, 2002), cannabis use should not be regarded as harmless. Studies indicate that exposure to cannabis can lead to a variety of adverse effects, many of which are associated with long term and heavy use of cannabis, including administration by smoking (e.g. chronic bronchitis, myocardial infraction), poor psychosocial functioning, cognitive impairments, psychotic symptoms and mental health disorders, cannabis dependence and other illicit drug use and dependence (Hall & Degenhardt, 2014; Lev-Ran et al., 2014; Volkow, Baler, Compton & Weiss, 2014). Acute adverse effects of cannabis exposure have also been reported, and research has found that one of the most common cannabis-related reasons for seeking emergency medical care is cannabis poisoning. Cannabis poisoning can present itself in various forms and can be caused by voluntary and involuntary exposure. The latter would be a case in which a cannabis product was ingested without the person exposed being aware that s/he was being exposed to the psychoactive substance. Cannabis poisoning often presents with acute anxiety, intermittent loss of consciousness or nausea (Heard, Marlin, Nappe & Hoyte, 2017). While most synthetic cannabinoid poisoning exposures are relatively benign, they have been associated with seizures, ischemic stroke and cardiac toxicity (Tait, Caldicott, Mountain, Hill & Lenton, 2016), especially newer products (Monte et al., 2014).

Changes in cannabis policies and cannabis use patterns (synthetic and plant-based) in the general and patient population may relate to changes in cannabinoid poisoning exposures. Research from the U.S. (Wood, 2013) and the U.K. (Wood, Hill, Thomas & Dargan, 2014) has shown increases in synthetic cannabinoid poisoning calls. In New Zealand, data from a poisoning center showed a decrease in calls related to synthetic cannabinoids after synthetic cannabis analogues were prohibited (Schep, Slaughter & Temple, 2011). Other studies from the U.S. have shown increases in cannabis poisoning exposures after legalization of medical and recreational cannabis use (Wang, Banerji, Contreras & Hall, 2019), and that children may be at particular risk for cannabis poisoning (Onders, Casavant, Spiller, Chounthirath & Smith, 2016; Richards, Smith & Moulin, 2017; Thomas et al., 2019; Wang et al., 2019; Wang, Roosevelt & Heard, 2013). Increases in cannabis poisoning cases have also been observed among children in France (Spadari et al., 2009).

The relatively high potency of medical cannabis and synthetic cannabinoid products can result in more pronounced clinical effects after exposure as compared to recreational cannabis exposure (Brents & Prather, 2014; Rosenbaum, Carreiro & Babu, 2012). Furthermore, MC patients tend to be relatively old (Fairman, 2016; Reinarman, Nunberg, Lanthier & Heddleston, 2011) and more likely than recreational cannabis users to be women (Sznitman, 2017), which suggests that there may be demographic differences in poisoning cases across the different cannabis and synthetic cannabinoid exposure categories. We are aware of only one study that has compared different types of cannabinoid poisoning. Using data from the Texas Poison Center Network, the study compared exposure to herbal cannabis and synthetic cannabinoid cases and found that the latter exposures were more likely to occur after administration through inhalation, to involve adults and to result in serious outcomes (Forrester, Kleinschmidt, Schwarz & Young, 2012). No distinction was made between medical and recreational cannabis exposures.

The current study

In light of the fact that many different countries are currently moving towards more liberal cannabis policies and changes in cannabis attitudes and use, it is crucial to investigate potential public health effects in various different contexts and to distinguish between different types of cannabis and synthetic cannabinoid exposures. Israel is an informative case study due to: (1) the observed increase in both medical and recreational cannabis use, (2) early legislation to prevent the use of synthetic cannabinoids, and (3) an established and comprehensive MC program. To further develop the evidence-base related to different types of cannabis and synthetic cannabinoid poisoning, we conducted a retrospective study evaluating Israeli national trends of cannabinoids (medical and recreational cannabis, synthetic cannabinoid) exposures between 2007 and 2018 stratified by medical, recreational and synthetic exposures. We also compare demographics and clinical context and effects for these three types of exposures.

Methods

A retrospective study was conducted based on data from the Israel Poison Information Center (IPIC) at the Rambam Health Care Campus. The method of operation of the IPIC has been reported elsewhere (Bentur et al., 2019). Briefly, the IPIC provides consultations in clinical toxicology, i.e., the rational management of the acutely poisoned patient. It serves the entire population of Israel and it is the only poison center in Israel that serves both the general public and healthcare facilities 24 h a day. Reporting to the IPIC is passive and not mandatory. Similarly to other national poison centers – cases reflect information provided when the public or healthcare professionals report an actual or potential exposure. The IPIC clinical staff comprises physicians and nurses. Most of the physicians are board certified in Internal Medicine, Pediatrics, and Clinical Pharmacology, and have received additional training in Clinical Toxicology. The nursing staff include experienced nurses, all of them with a masters' degree and graduates of an intensive care or emergency medicine course, including special training from IPIC physicians. Consultations include providing advice on first aid, triage, evaluation, management and follow up. Additional activities of the IPIC include providing drug and reproductive toxicology information, teaching clinical toxicology, collecting epidemiologic data, national preparedness to multi-casualty toxicological incidents, research, and laboratory services.

The annual number of calls to the IPIC has been increasing from 31,000 calls in 2007 to 40,000 in 2018. This amounts to 432 calls per 100,000 population in 2007 and 446 calls per 100,000 population in 2018. All calls are documented in a designated toxicological computerized database and classified according to a pre-existing list of categories, classifications, and sub-classifications. The database is

Table 1
Demographic factors, exposure circumstances and clinical effects by recreational, medical and synthetic cannabinoid exposure cases reported to the Israel Poison Information Center.

	Total (n = 615, 100%)	Recreational cannabis (n = 337, 54.8%)	Synthetic cannabinoids (n = 205, 33.3%)		Medical cannabis (n = 73, 11.9%)	
	n (%)	n (%)	n (%)	Unadjusted RRR	n (%)	Unadjusted RRR
Demographics						
Child/adolescent	132 (21.5)	78 (23.1)	44 (21.5)		10 (13.7)	
Adult	483 (78.5)	259 (76.9)	161 (78.5)	1.06	63 (86.3)	1.87
Male	433 (70.4)	224 (66.5)	175 (84.4)	3.06***	34 (46.6)	0.45**
Female	182 (29.6)	113 (33.5)	30 (14.6)		39 (53.4)	
Caller						
Health care provider	476 (76.9)	250 (73.7)	189 (91.7)		37 (50.0)	
Public	143 (23.1)	89 (26.3)	17 (8.3)	0.25***	37 (50.0)	2.62***
Co-use						
No co-use	510 (83.5)	267 (80.2)	176 (85.9)		67 (91.8)	
Co-use	101 (16.5)	66 (19.8)	29 (14.1)	0.7	6 (8.2)	0.36*
Clinical effects						
Severity						
No/minor effect	427 (71.9)	239 (73.8)	134 (66.7)		54 (78.3)	
Moderate/major effect	167 (28.1)	85 (26.2)	67 (33.3)	1.4	15 (21.7)	0.78
Clinical manifestations						
Cardiovascular	217 (36.0)	109 (33.3)	89 (43.4)	1.55**	19 (27.1)	0.76
Gastrointestinal	141 (23.3)	42 (12.8)	79 (38.3)	4.27***	20 (28.6)	2.74**
Neurological	349 (60.0)	180 (57.1)	124 (62.3)	1.26	45 (66.2)	1.49
Psychiatric	53 (8.8)	36 (11.0)	14 (6.8)	0.6	3 (4.3)	0.37
Management site						
Emergency Department	359 (59.6)	192 (58.7)	131 (63.6)		36 (52.2)	
Hospital Admission	130 (21.6)	67 (20.5)	51 (24.8)	1.13	12 (17.4)	0.97
Community Clinic	67 (11.1)	37 (11.3)	18 (8.7)	0.72	12 (17.4)	1.75
On-site	46 (7.6)	31 (9.5)	6 (2.9)	0.29**	9 (13.0)	1.57

Note: RRR = Relative Risk Ratio.
* $P \leq 0.05$,.
** $P \leq 0.01$,.
*** $P \leq 0.001$.
Child/adolescents were 0–17 years of age, adults were 18+ years of age.

maintained and updated by the IPIC team. Exposures to medical, recreational and synthetic cannabinoid compounds are classified as pharmaceuticals/drugs of abuse in the IPIC database. The search terms to identify cannabinoid exposure cases were chosen from a previously prepared list of classifications and sub-classifications available at the IPIC and the search included the years 2007–2018. For the denominators, search methodology included the keywords “pharmaceuticals” and “drugs of abuse” and within these categories the search terms “cannabis” and "cannabinoids" were used. The identified cases were manually reviewed by trained research assistants and coded as medical, recreational or synthetic cannabinoid exposure according to the type of cannabinoid exposure recorded in the medical chart. Of the identified cases (n = 868), 71 were excluded for reasons of insufficient data related to type of cannabinoid exposed to and information calls without exposure. Data were extracted manually into an electronic spreadsheet (Excel 2016, Microsoft). Analyses were conducted in SPSS v.25. (SPSS, 2017). The Institutional Review Board (Helsinki Committee) of Rambam Health Care Campus approved the study.

Variables

Cannabinoid exposures were categorized into recreational and medical cannabis and synthetic cannabinoid exposures. Yearly population rate of exposure for each type of cannabinoid exposure was calculated by dividing the total number of poisoning cases by the Israeli population in each year. Population rates were scaled to 100,000 people.

Demographic data collected for each poisoning case included patients’ age and gender. There were only 2 exposures for synthetic cannabinoids in the age group 0–5, therefore the age variable was coded as child/adolescent (0–17 years) vs. adult (18 and above years). Data on the caller included whether the person making the call was a health care provider or member of the public. In addition, each case was coded for whether or not cannabinoid exposure co-occurred with other substances of abuse. Management site recommended by the IPIC clinical toxicologist working was coded with the following categories: emergency department (ED), hospital admission, community clinic (ambulatory), on site. Clinical effects were measured by the severity of exposure. Poison center staff classified exposure cases according to the following criteria: no effect (no clinical manifestations due to exposure), minor effect (some minimally troublesome manifestations), moderate effect (more pronounced, prolonged manifestations), major effect (manifestations that are life-threatening or cause significant disability or disfigurement) (Bentur et al., 2019). However, since the variable had a skewed distribution with few cases in the minor and the major categories, the variable was dichotomized to no effect/minor effect vs. moderate/major effect. The clinical evaluation of patients was coded according to the following four domains that are routinely assessed at the IPIC using a system oriented approach: gastrointestinal, cardiovascular, neurological, and psychiatric. We assess all of these as the different cannabinoid affinity to receptors, coupled with their relative concentrations, may result in different manifestations or body system affected.

Statistical analyses

Univariate multinomial logistic regression analysis was used to assess the unadjusted relative risk ratios (RRR) of demographic and clinical factors for the three cannabinoid poisoning types. The recreational cannabis exposure group was the reference category in these analyses. The significance threshold was set to α = 0.05, and testing was 2-sided. We describe the trends in rates of the three categories of cannabinoid poisoning by plotting the data over time.

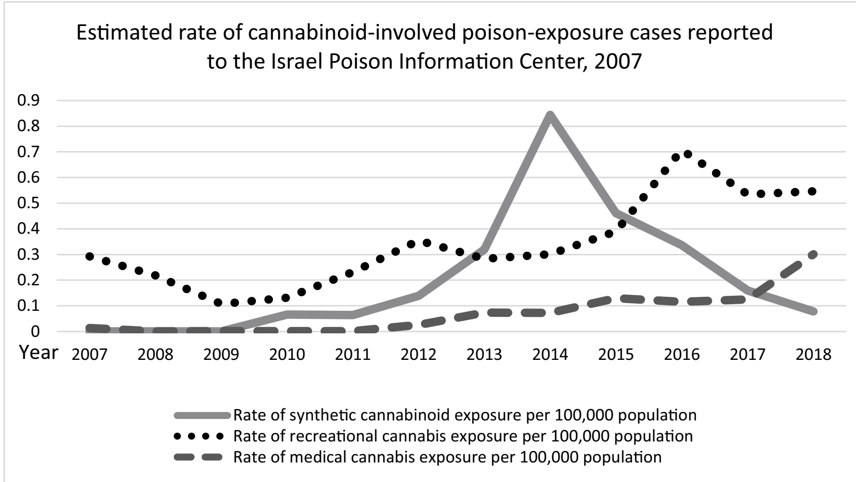

Fig. 1. Estimated rate of cannabinoid-involved poison-exposure cases reported to the Israel Poison Information Center, 2007–2018.

Results

Demographic factors, exposure circumstances and clinical effects

Overall, there were 615 cannabinoid exposure cases which represented 21.0% of all pharmaceutical and illicit substance abuse poisoning cases in the time period. There were 337 (54.8%) recreational cannabis exposures, 205 (33.3%) synthetic cannabinoid exposures, and 73 (11.9%) MC exposures. Demographic data and exposure circumstances stratified by type of cannabinoid exposure are presented in Table 1. The mean age of the sample was 27.79 years (range: 0–95, Standard Deviation [S.D.] 16.20), and there were no significant age differences across the three cannabinoid exposure groups. Males accounted for 70.0% of all poisoning exposures, with synthetic cannabinoid exposure cases more likely to be male than cannabis cases (RRR = 3.06, $p < 0.001$); MC cases were less likely than recreational cannabis cases to be male (RRR = 0.45, $p \leq 0.01$).

The minority of the calls (23.0%) were made by the public. Compared to recreational cannabis cases, synthetic cannabinoid exposures were less likely to be called in by the public (RRR = 0.25, $p \leq 0.001$) whereas MC cases were more likely to be called in by the public (RRR = 2.62, $p \leq 0.001$).

The majority of exposures had no co-use of other illicit substances (83.5%), with MC exposure cases being less likely than recreational cannabis cases to present with co-use (RRR = 0.36, $p \leq 0.05$). The main other co-used drugs, as reported by the patients or identified in urine toxicology assays, included ethanol, caffeine, opioids, benzodiazepines, LSD, cathinone, volatile substances (e.g., glue sniffing), cocaine, Ecstasy, methamphetamines, and amphetamines. In terms of severity, the most common outcome was no/minor effect (71.9%) with no significant difference between the three groups of cannabinoid exposures ($p > 0.05$).

The most common body system reported to be affected was neurological (60.0%) with no significant difference between type of cannabinoid exposure ($p > 0.05$). Synthetic cannabinoid exposures were more likely to present with both cardiovascular (RRR = 1.55, $p \leq 0.01$) and gastrointestinal (RRR = 4.27, $p \leq 0.001$) manifestations than recreational cannabis exposure cases. MC cases were more likely than recreational cannabis cases to present with gastrointestinal manifestations (RRR = 2.74, $p \leq 0.01$).

Most of the cases (59.6%) were referred to the ED for observation and management. There were few differences in terms of management site for the three types of exposure cases. In fact, the only significant difference was for on-site treatment, which was less common for synthetic cannabinoid cases compared to recreational cannabis cases (RRR = 0.29, $p \leq 0.01$).

Sensitivity analyses

The clinical manifestations and severity reflects the patient's condition at the time of consultation and in some cases misses the peak effect, which may lead to an underestimation of the severity of the clinical condition. In the current data, the time elapsed since cannabinoid exposure was unknown for 34.0%. Nevertheless, for cases with complete data, results show that compared to recreational cannabis exposure cases, synthetic cannabinoid cases were more likely to turn to the IPIC after 7 or more hours had elapsed (RRR = 1.72, $p \leq 0.05$) and MC cases were less likely to turn to the IPIC after 7 or more hours post exposure (RRR = 0.32, $p \leq 0.01$).

To examine whether clinical outcomes were different across the three cannabinoid exposure types after control for time elapsed, we calculated a multinomial logistic regression model where time elapsed, severity and clinical manifestations were entered as independent variables, and the three types of cannabinoid exposures were entered as the dependent variable. Results from these models confirm the results from the unadjusted multinomial logistic regression models. There were no significant differences between the three types of cannabinoid exposure in terms of severity and cardiovascular and neurological manifestations, while synthetic cannabinoid exposures were more likely to present with both cardiovascular (RRR = 1.62, p = 0.051) and gastrointestinal (RRR = 4.91, $p \leq 0.001$) manifestations and MC cases were more likely to present with gastrointestinal manifestations (RRR = 2.79, $p \leq 0.01$).

Time trends in cannabinoid poisoning exposures

Fig. 1 shows the time trend for the different types of cannabinoid exposures. While the rate of recreational and MC exposures increased relatively steadily over the study period, the figure shows a very different pattern for the rate of synthetic cannabinoid cases. Specifically, after a period of almost no synthetic cannabinoid exposure cases in the beginning of the study period, the rate of synthetic cannabinoid exposure cases increased substantially, reaching levels higher than both medical and recreational cannabis exposure cases in 2014. After this period, synthetic cannabinoid cases drop off sharply, and in 2018 there were less synthetic cannabinoid cases than both medical and recreational cannabis cases.

Discussion

Similar to what has been reported elsewhere (Fairman, 2016; Forrester et al., 2012; Forrester, Kleinschmidt, Schwarz & Young, 2011;

Hoyte et al., 2012; Salas-Wright, Carbone, Holzer & Vaughn, 2019; Whitehill et al., 2019; Wood, 2013), the majority of all three types of cannabinoid exposure cases were male. This is not surprising in light of the fact that men tend to be more likely to use cannabis and other illicit substances than women (Degenhardt et al., 2008). The fact that MC cases were less likely to be male than recreational cannabis cases also echoes previous research from Israel that has shown that the skewed gender distribution in cannabis use is less stark among medical users than among recreational cannabis users (Sznitman, 2017).

The differences observed in terms of the source of calling in the exposure case might be related to the public's perceived risk associated with admitting to cannabinoid exposure. Indeed, the synthetic cannabinoid exposures were the least likely to be called in by the public, which might relate to the fact that legislation was put in place and enforced early on which in turn may have sent signals that synthetic cannabinoids are illegal and will be sanctioned. This stands in contrast to MC cases, which were most likely to be called in by the public. The legal status of MC use in Israel might make the public more willing to report cases of exposure and poisoning from this substance than other types of illegal cannabinoids.

Despite a great deal of concern related to high potency cannabinoids associated with synthetic and medical cannabinoid exposures, the results presented in this study show that there were no greater adverse effects associated with these cannabinoid poisoning exposure cases. This is contrary to a study based on U.S. poison-exposure data that found synthetic cannabinoid cases to have more severe effects compared to herbal cannabinoid exposure cases (Forrester et al., 2012). However, our data echo findings from the U.S. that show that the majority of all types of cannabinoid poisoning cases have minor adverse signs and symptoms (Hoyte et al., 2012; Whitehill et al., 2019).

Gastrointestinal manifestations were more common for synthetic cannabinoids and MC exposure compared to recreational cannabis exposure, and cardiovascular manifestations were also more common among synthetic cannabinoid cases compared to recreational cannabis cases. The underlying reasons for these differences are unclear, and the current data do not enable an investigation into the mechanisms for these findings. More research in this area is warranted.

Although most people who use cannabis will not experience clinical or social problems (Eisen et al., 2002; von Sydow et al., 2001; Wagner & Anthony, 2002), cannabis consumption carries some risk of adverse consequences, including poisoning as shown in the current study. It is, however, important to point out that the majority of the cases were of minor severity and that the moderate to major severity exposures might be overestimates. Indeed, it is possible that poison center data are biased towards severe cases as less severe cases might be less likely to be reported. As such, the current study suggests that exposure to all types of cannabinoids rarely produce severe clinical toxicity.

Yet, acute detrimental effects of cannabis, such as poisoning, do occur and when they do they cause suffering to individuals and cost to the health care system. It is commonly accepted that if a greater percentage of the general population consume cannabis, even a small risk of adverse effects may have significant deleterious consequences for the health of the population (Rose, 1992). The current study findings are in agreement with this "single distribution theory" in that it shows that during a period with increasing use of both medical and recreational cannabis, there have also been increases in poisoning cases related to exposure to these types of cannabinoids. Similar increases have been found following medical and recreational cannabis legalization in the U.S. (Onders et al., 2016; Richards et al., 2017; Thomas et al., 2019; Wang et al., 2019). One interpretation of the results is that liberal cannabis policies, which lead to more access to cannabis, are detrimental to public health and that more effort is needed to curb the use of average population level use. However, such a conclusion must be weighed up against the fact that cannabis use, in addition to its potential harmful effects, is also used to ease suffering from various medical symptoms (Abrams, 2018). It must also be weighed up against research evidence that suggests that population wide increases in cannabis use is related to population level reductions in opioid use and related adverse effects (Bachhuber, Saloner, Cunningham & Barry, 2014), which are more severe than the adverse effects related to exposure to cannabis. Yet, not all research has found such an association (Shover, Davis, Gordon & Humphreys, 2019). Finally, it must be weighed up against the potential negative effects of criminal penalties for individuals using a relatively low toxic substance such as cannabis (e.g. stigma, cost to the criminal justice system).

Lastly, the current study suggests that providing authorities tools to minimize the availability of synthetic cannabinoids is related to rates of poisoning. Indeed, the rate of synthetic cannabinoid cases increased in the first part of the study period. After 2014, and thus one year after the enactment of a new Israeli law that provided authorities tools to minimize the manufacture and distribution of synthetic cannabinoids, synthetic cannabinoid cases sharply decreased. This findings echoes previous research from New Zealand that found reduction in synthetic cannabinoid poisoning cases after synthetic cannabis analogues were prohibited (Schep et al., 2011).

Limitations

Similar to other studies using national poison center data, data from IPIC have limitations that should be considered when attempting to interpret these results. IPIC data rely on the quality and accuracy of data reported by the public and on information provided by the clinician contacting the poison center. Ascertainment of the data provided is limited. The IPIC attempts to follow up moderate to severe cases, but this might be limited, especially in the drug abuse population (Bentur, Bloom-Krasik & Raikhlin-Eisenkraft, 2008). The data is, however, improved by using predesigned and standardized data collection forms within electronic databases. In addition to the quality of data provided, patients exposed to drugs of abuse are often reluctant to seek medical attention and thus the data may under-estimate the true occurrence of cannabinoid cases. Additionally, and as already mentioned in the discussion above, the cases that are reported may be biased towards more severe cases.

It would have been informative to calculate the rate of poisoning cases per total number of users in each of the three cannabinoid groups included in the analyses. This was, however, not feasible as we do not have estimates of number of recreational and synthetic cannabinoids users during the time points we are studying.

The final issue relates to power and the small sample size that may have limited our power to detect statistically significant differences between exposure groups and it also limited the advanced statistical modeling available. Indeed, the small sample size informed our decision to keep analyses at the descriptive and univariate level, akin to what has been done in previous reports on cannabinoid poisoning exposures with similar small sample sizes (Forrester et al., 2012; Thomas et al., 2019; Wang et al., 2019). The implication of the small data size is that interpretation of these results should be done with caution and conclusions need to be confirmed in future follow-up studies with data from more years. It is, however, still important to make use of the data at this moment in time, despite the data limitations. This is because cannabis policy and cannabis use is changing rapidly. The current study, combined with other similar studies, can be used to build a much needed evidence-base for the effects of cannabis use and cannabis policy on poisoning.

Conclusion

In sum, the findings presented in this paper show that time trends in cannabinoids cases run parallel to changes in cannabis policy, legislation and cannabis use patterns. Yet, one must exercise caution when using ecological correlations, as those presented here, to draw causal, individual-level conclusions. Furthermore, even if future studies conclude that cannabis policies have direct effects on cannabinoid poisoning, the policy implications are unclear. This is because the severity of poisoning cases tend to be minor and, in addition to adverse effects such as poisoning, cannabis use is also associated with positive health effects on the individual and population level. The complex picture of cannabis as having both beneficial and detrimental effects on health certainly complicates the public health message and public health and criminal justice approaches to cannabis use and its derivatives. One potential way forward is to adopt a similar approach to what has been done in the context of alcohol (Grønbæk, 2009), namely to develop guidelines for sensible use of cannabis and to launch public prevention campaigns that aim to limit but not necessarily totally prevent all forms of cannabis use. In parallel, more research on positive and negative health outcomes associated with cannabis use is needed in order to better inform policies as to the best way to protect the public from both physical harm and unnecessary societal cost. In jurisdictions with liberal cannabis policies and increased public exposure to cannabinoids, training of physicians and other health care professionals related to cannabinoid poisoning may be particularly important.

Credit author statement

Sharon R. Sznitman participated in the conceptualization and design of the study as well as the analysis and interpretation of data. Sznitman has lead the drafting of the article.

Lianna Pinsky-Talbi participated in the conceptualization and design of the study as well as the analysis and interpretation of data.

Maisar Salameh substantially contributed to the acquisition of data and drafting the paper.

Taleb Moed substantially contributed to the acquisition of data and drafting the paper.

Yedidia Bentur participated in the conceptualization and design of the study as well as the analysis and interpretation of data.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2020.102711.

References

Abrams, D. I. (2018). The therapeutic effects of cannabis and cannabinoids: An update from the national academies of sciences, engineering and medicine report. *European Journal of Internal Medicine, 49*, 7–11.

Bachhuber, M. A., Saloner, B., Cunningham, C. O., & Barry, C. L. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the united states, 1999-2010. *JAMA Internal Medicine, 174*, 1668–1673.

Bentur, Y., Bloom-Krasik, A., & Raikhlin-Eisenkraft, B. (2008). Illicit cathinone (“Hagigat”) poisoning. *Clinical Toxicology (Philadelphia, Pa.), 46*, 206–210.

Bentur, Y., Lurie, Y., Cahana, A., Bloom-Krasik, A., Kovler, N., & Neuman, G. (2019). Poisoning in Israel: Annual report of the Israel poison information center, 2017. *Israel Medical Association Journal, 21*, 175–182.

Brents, L. K., & Prather, P. L. (2014). The K2/Spice phenomenon: Emergence, identification, legislation and metabolic characterization of synthetic cannabinoids in herbal incense products. *Drug Metabolism Reviews, 46*, 72–85.

Brewer, T. L., & Collins, M. (2014). A review of clinical manifestations in adolescent and young adults after use of synthetic cannabinoids. *Journal for Specialists in Pediatric Nursing, 19*, 119–126.

Degenhardt, L., Chiu, W.-T., Sampson, N., Kessler, R. C., Anthony, J. C., & Angermeyer, M. (2008). Toward a global view of alcohol, tobacco, cannabis, and cocaine use: Findings from the WHO world mental health surveys. *PLOS Medicine, 5*, e141.

Eisen, S. A., Chantarujikapong, S., Xian, H., Lyons, M. J., Toomey, R., & True, W. R. (2002). Does marijuana use have residual adverse effects on self-reported health measures, socio-demographics and quality of life? A monozygotic co-twin control study in men. *Addiction, 97*, 1137–1144.

Fairman, B. J. (2016). Trends in registered medical marijuana participation across 13 US states and District of Columbia. *Drug and Alcohol Dependence, 159*, 72–79.

Fattore, L., & Fratta, W. (2011). Beyond THC: The new generation of cannabinoid designer drugs. *Frontiers in Behavioral Neuroscience, 5*.

Forrester, M. B., Kleinschmidt, K., Schwarz, E., & Young, A. (2011). Synthetic cannabinoid exposures reported to Texas poison centers. *Journal of Addictive Diseases, 30*, 351–358.

Forrester, M. B., Kleinschmidt, K., Schwarz, E., & Young, A. (2012). Synthetic cannabinoid and marijuana exposures reported to poison centers. *Human & Experimental Toxicology, 31*, 1006–1011.

Grønbæk, M. (2009). The positive and negative health effects of alcohol- and the public health implications. *Journal of Internal Medicine, 265*, 407–420.

Hall, W., & Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. *Drug Testing and Analysis, 6*, 39–45.

Harel-Fisch, Y. (2017). Dramatic increase in cannabis use among young and adult populations in Israel: The “normalization” effects of the intense public debates regarding cannabis legalization and medicalization. *Lisbon Addictions* Lisbon, Portugal.

Heard, K., Marlin, M. B., Nappe, T., & Hoyte, C. O. (2017). Common marijuana-related cases encountered in the emergency department. *American Journal of Health-System Pharmacy, 74*, 1904–1908.

Hoyte, C. O., Jacob, J., Monte, A. A., Al-Jumaan, M., Bronstein, A. C., & Heard, K. J. (2012). A characterization of synthetic cannabinoid exposures reported to the national poison data system in 2010. *Annals of Emergency Medicine, 60*, 435–438.

Isralowitz, R., & Reznik, A. (2018). Cannabis use in Israel: A cross sectional overview of multiple study groups. *International Journal of Mental Health and Addiction, 16*, 832–842.

Kahana, E. (2019). *Poison in a pretty package: The law against synthetic drugs.* Israeli Anti-Drug Authorathyhttps://www.gov.il/BlobFolder/reports/ie_17_synthetic_drugs/en/Poison%20in%20a%20Pretty%20Package.pdf.

Lev-Ran, S., Roerecker, M., Le Foll, B., George, T. P., McKenzie, K., & J., R. (2014). The association between cannabis use and depression: A systematic review andmeta-analysis of longitudinal studies. *Psychological Medicine, 44*, 797–810.

Monte, A. A., Bronstein, A. C., Cao, D. J., Heard, K. J., Hoppe, J. A., & Hoyte, C. O. (2014). An outbreak of exposure to a novel synthetic cannabinoid. *The New England Journal of Medicine, 370*, 389–390.

Onders, B., Casavant, M. J., Spiller, H. A., Chounthirath, T., & Smith, G. A. (2016). Marijuana exposure among children younger than six years in the United States. *Clinical Pediatrics, 55*, 428–436.

Reinarman, C., Nunberg, H., Lanthier, F., & Heddleston, T. (2011). Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs, 43*, 128–135.

Reiss, J., & Harel-Fish, J. (2017). *Patterns of use of alcohol and drugs in Israel, data from 2015 to 2016 [in Hebrew].* Israeli Anti-Drug Authority.

Richards, J. R., Smith, N. E., & Moulin, A. K. (2017). Unintentional cannabis ingestion in children: A systematic review. *The Journal of Pediatrics, 190*, 142–152.

Rose, G. (1992). *The strategy of preventive medicine.* Oxford: Oxford University Press.

Rosenbaum, C. D., Carreiro, S. P., & Babu, K. M. (2012). Here today, gone tomorrow…and back again? A review of herbal marijuana alternatives (K2, spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. *Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology, 8*, 15–32.

Salas-Wright, C. P., Carbone, J. T., Holzer, K. J., & Vaughn, M. G. (2019). Prevalence and correlates of cannabis poisoning diagnosis in a national emergency department sample. *Drug and Alcohol Dependence, 204*, 107564.

Schep, L. J., Slaughter, R. J., & Temple, W. A. (2011). Synthetic cannabinoid use in New Zealand: A brief evaluation of inquiries to the New Zealand National poisons centre. *New Zealand Medical Journal, 124*, 99–101.

Shover, C. L., Davis, C. S., Gordon, S. C., & Humphreys, K. (2019). Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proceedings of the National Academy of Sciences, 116*, 12624–12626.

Spadari, M., Glaizal, M., Tichadou, L., Blanc, I., Drouet, G., & Aymard, I. (2009). Intoxications accidentelles par cannabis chez l’enfant : Expérience du centre antipoison de Marseille. *La Presse Médicale, 38*, 1563–1567.

SPSS, I. (2017). *SPSS base 25.0 for windows user's guide.* Chicago SPSS Inc.

Sznitman, S. R. (2017). Do recreational cannabis users, unlicensed and licensed medical cannabis users form distinct groups? *International Journal of Drug Policy, 42*, 15–21.

Tait, R. J., Caldicott, D., Mountain, D., Hill, S. L., & Lenton, S. (2016). A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology, 54*, 1–13.

Thomas, A. A., Von Derau, K., Bradford, M. C., Moser, E., Garrard, A., & Mazor, S. (2019). Unintentional pediatric marijuana exposures prior to and after legalization and commercial availability of recreational Marijuana in Washington State. *The Journal of Emergency Medicine, 56*, 398–404.

UNODC. (2017). *World drug report.* New York: United Nations.

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. B. (2014). Adverse health effects of marijuana use. *The New England Journal of Medicine, 370*, 2219–2227.

von Sydow, K., Lieb, R., Pfister, H., Höfler, M., Sonntag, H., & Wittchen, H.-U. (2001). The natural course of cannabis use, abuse and dependence over four years: A longitudinal community study of adolescents and young adults. *Drug and Alcohol Dependence,, 64*, 347–361.

Wagner, F. A., & Anthony, J. C. (2002). From first drug use to drug dependence:

Developmental periods of risk for dependence upon Marijuana, Cocaine, and Alcohol. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 26*, 479–488.
Wang, Banerji, S., Contreras, A., & Hall, K. (2019). Marijuana exposures in Colorado, reported to regional poison centre, 2000–2018. *Injury Prevention* injuryprev-2019-043360.
Wang, Roosevelt, G., & Heard, K. (2013). Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatrics, 167*, 630–633.
Wells, D. L., & Ott, C. A. (2011). The "New" marijuana. *Annals of Pharmacotherapy, 45*, 414–417.
Whitehill, J. M., Harrington, C., Lang, C. J., Chary, M., Bhutta, W. A., & Burns, M. M. (2019). Incidence of pediatric Cannabis exposure among children and teenagers aged 0 to 19 years before and after medical marijuana legalization in Massachusetts. *JAMA Network Open, 2* e199456-e199456.
Wood (2013). Exposure to bath salts and synthetic tetrahydrocannabinol from 2009 to 2012 in the United States. *The Journal of Pediatrics, 163*, 213–216.
Wood, Hill, S. L., Thomas, S. H., & Dargan, P. I. (2014). Using poisons information service data to assess the acute harms associated with novel psychoactive substances. *Drug Testing and Analysis, 6*, 850–860.
Zarhin, D., Negev, M., Vulfsons, S., & Sznitman, S. R. (2018). Rhetorical and regulatory boundary-work: The case of medical cannabis policy-making in Israel. *Social Science & Medicine, 217*, 1–9.