AN OBSERVATIONAL STUDY OF CANNABIS EXPOSURES REPORTED TO THE POISONS INFORMATION HELPLINE OF THE WESTERN CAPE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine (Emergency Medicine)

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Contents

Candidates' declaration

I, Jakobus Kritzinger Venter declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (Emergency Medicine) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University. I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong. I confirm that the work submitted for assessment of the above degree is my own unaided work except where I have explicitly indicated otherwise. I have followed the required conventions in referencing the thoughts and ideas of others. I understand that the University of the Witwatersrand may take disciplinary action against me if there is belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing. I have included as an appendix a report from Turnitin indicated the level of plagiarism in my research document

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The …… day of ……. 2021

Dedication

I would like to thank Dr Alison Bentley, Dr Sashen Murugan and Dr Cindy Stephen for their guidance, mentorship, and assistance. I would like to dedicate this thesis to my wife Dina, and daughter Annelize.

Chapter 1: Research protocol

Title

An observational study of cannabis exposures reported to the Poison Information Helpline of the Western Cape

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Literature review

Cannabis is a popular drug mainly used for recreational and religious purposes. According to a research report published by the South African Community Epidemiology Network on Drug Use (SACENDU) that studied national data from 1996 to 2015, cannabis abuse accounted for the most admissions to specialist drug treatment facilities in South Africa and is most commonly the cause for substance abuse admissions in under 20-year-olds.[1] This is representative of recreational cannabis use only. No reports are currently available on the demographics of cannabis use for medical purposes in South Africa.

Cannabis contains over 240 cannabinoid compounds of which 60 have a physiological effect on the endocannabinoid system. The main cannabinoid compounds are delta -9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is mostly sought after for recreational use and is responsible for the psychotropic, or the 'high' effects of cannabis. CBD is the focal point of medical marijuana treatment for its effects on pain pathways and appetite. Two main endocannabinoid receptors have been described, Cannabinoid Receptor 1

(CB1) and Cannabinoid Receptor 2 (CB2). CB1 receptors are mainly found in the central nervous system, gastrointestinal tract, and endocrine glands. The psychotropic effects of cannabis are produced via CB1 receptor antagonism. CB2 receptors are mainly found in organs responsible for immunological function, and do not have any psychotropic effects. Cannabis's anti-emetic effects are mediated via 5-HT3 receptors, and not via CB receptors.[2,3]

Natural cannabis forms include dried plant products or manufactured products like cannabis oil. The sale of natural cannabis products is still prohibited in South Africa, but growing cannabis for private use is legal, and cannabis oil can be easily manufactured at home without specialised equipment. The sale of CBD-based health remedies is legal in South Africa and CBD products are available over the counter. Natural forms of medical cannabis are thus freely available, compared to synthetic and other pharmacological grade cannabis products, which can only be accessed via a section 21 application to the South African Health Products Regulatory Authority (SAHPRA). Compared to pharmacological-grade cannabis products, levels of cannabinoid compounds found in natural forms are difficult to regulate, and these products are rarely cultivated purely for medical use. Exposure to easily accessible and poorly regulated medical cannabis products puts consumers at risk, leading to unwanted adverse effects.[2–5]

Medical cannabis differs from recreational cannabis. It is formulated to contain a known ratio of cannabinoid compounds. Medical cannabis is available in different forms. The semi-synthetic forms include products like Sativex, a pharmacological grade natural plant extract containing a 1:1 ratio of THC and CBD that is registered for the treatment of multiple sclerosis. Synthetic forms contain synthetically made cannabinoids, resulting in a more predictable therapeutic effects compared to natural forms. Examples include Dronabinol, a synthetic THC compound registered for chemotherapy-induced nausea and vomiting, and

Epidiolex, a synthetic CBD-based medication, is registered for the treatment of rare paediatric seizure disorders like Lennox Gastaut and Dravet syndrome.[2,4,5] Dronabinol was previously registered in South Africa under the name Marinol but has since been discontinued. None of the other above-mentioned agents are currently registered in South Africa.

Many indications for taking cannabis as a medical therapy have been published in scientific journals as well as in the popular press and social media. A recent meta-analysis found cannabinoids to be beneficial in the management of the following conditions - chronic pain and spasticity, chemotherapy-induced nausea and vomiting, and HIV associated weight loss. The same article also warned that cannabinoids were associated with an increased risk of adverse effects when using any type of medical cannabis as opposed to placebo.[6]

In September 2018, the Constitutional Court decriminalised the use of cannabis products for private use. The right to privacy as guaranteed by Section 14 of the Constitution was found to be inconsistent with the following two acts: The Drugs Act (Section 4(b) and 5(b) of the Drugs and Drug Trafficking Act, 1992) that regulates public access and use of controlled and illegal substances, and the Medicines Act (Section 22A(9)(a)(i) of the Medicines and Related Substances Control Act, 1965, read with Schedule 7) that regulates pharmacological and non-pharmacological treatments as stipulated in the Schedules of Medicines. [7] Parliament was given 24 months to amend the constitution accordingly, and 2 interim Acts were read in during the ruling:

It is not a criminal offence for an adult person: to use or be in possession of cannabis in private for his or her personal consumption in private or to cultivate cannabis in a private place for his or her personal consumption in private.[7]

The public use, sale or commercialisation of cannabis and cannabis related products was not decriminalised. The ruling failed to address the use of cannabis products for medicinal

purposes. Use of cannabis for medical purposes was limited to those who could grow their own cannabis.

In 2020 the Cannabis for Private Purposes Bill[8] was introduced to the South African parliament. This bill defines what amount of cannabis is considered legal, and in what environment it can legally be consumed. The bill also makes provision for public safety, prohibiting the exposure of minors and non-consenting adults to cannabis products, as well as prohibiting the operation of a vehicle under the influence of THC. The bill, if passed in its current form, does not make provision for the commercialisation and sale of cannabis for recreational purposes, nor does it add new legislation with regards to cannabis as a medical therapy. At the time of writing, this bill has not yet passed.

Cannabis as a medical therapy is regulated by the Medicines and Related Substance Act of 1965 (Medicines Act), and the Schedule of Medicine as set out by SAHPRA. The following schedules are listed for various cannabis products and cannabinoid compounds - cannabis plant material, synthetic cannabinoids and THC are listed as a schedule seven substance. Dronabinol is listed as a schedule six substance. CBD is listed as a schedule four substance.[5] In May 2019, the Minister of Health made an amendment to the Medicines Act, excluding certain preparations containing CBD from the Schedule of Medicines. Preparations that contain a maximum daily dose of 20mg CBD, with an accepted low-risk claim, and indicated for general health enhancement or maintenance are excluded from the Schedule of Medicine. Products may only contain cannabinoids found in natural cannabis products with set limits of THC (0.001%) CBD (0.0075%) content. Preparations that do not comply with these guidelines still fall under the previously listed medicine schedule.[9]

The study of cannabis in the general population is wrought with ethical difficulties. Ethical concerns can be grouped into 3 categories - regulatory concern, physician concern, and public

concern. Due to regulation, the benefit of cannabinoid containing health products will be difficult to study as none are available commercially. There is also a lack of unanimity between legal and regulatory bodies. Cannabis users may thus not report health benefits nor side effects for fear of legal repercussions. Physicians may be loath to prescribe or distribute cannabis products due to either unfamiliarity or concern for toxic effects. Long term effects and addiction is of special concern. Furthermore, physicians are ethically bound to prescribe medicine only when a clear health benefit exists. This causes concern when providing cannabis therapy for conditions where the health benefit is not proven. A clear bias also exists in the public with regards to its presumed efficacy, health benefits and side effects. Any attempts to study cannabis use patterns in the general population will amplify this bias.[10]

The potency of cannabis products is difficult to monitor due to non-standardised testing. Cannabis potency is classified according to the THC to CBD ratio. A higher ratio indicates a more potent sample. A recent study examined the potency of commercial cannabis products in Washington state and found significant differences reported in THC/CBD ratios due to a lack of standardised protocols used by individual laboratories.[11] Furthermore, the levels of CBD and THC reported in commercial products may not be accurate. A review of 14 commercially available CBD based oil preparations regulated by European legislation found that 9 out of the 14 samples had concentrations that differed from the declared amount.[12] In South Africa, access to testing of CBD and THC levels in commercial products are limited, leaving consumers at risk and unable to make appropriately informed decisions, especially when using cannabis for its health benefits.

The expectation was that changing legislation and decriminalising cannabis use would lead to increased use of cannabis products. However, a direct link between legalization and increased cannabis use is not supported by recent international publications. State-level data from the National Survey on Drug Use and Health in the United States of America between 2002 and

2009, found a limited causal association between medical cannabis laws and increased cannabis use. [13] Similarly, by studying data from the Youth Risk Behavioural Surveillance Survey in the United States of America between 1991 and 2011, there was no increase in adolescent cannabis use related to the legalization of medical cannabis.[14]

In contrast to this, multiple studies reported an increase in cannabis-associated emergency department visits that correlates with changes in cannabis legalisation. An analysis of national data from the Drug Abuse Warning Network in the United States of America found that emergency department visits for monosubstance cannabis use increased from 51 to 79 visits per 100,000 visits between 2004 and 2011, and emergency department visits for cannabis as a component of polydrug use increased from 63 to 100 per 100,000 visits. The age group with the largest increase of emergency department visits was adolescents between 12 and 17 years of age.[15] A retrospective review of ICD codes in Colorado reported a rate of increase, from 1.8 per 1000 in 2009 to 4.9 per 1000 in 2015 of cannabis-related presentations to local emergency departments and urgent care units.[16] However, cannabis use patterns in South Africa are different from the United States of America, and these examples may not be applicable.

Publications of international poison centre data also show an increase in cannabis exposures associated with the ease of legal restrictions.[17] A review of reports of cannabis exposures to the Israeli Poison Information Centre found an increase in both recreational and medicinal cannabis use across all age groups from 2007 to 2018.[18] A review of the American Association of Poison Control Centre's national poison data system from 2005 to 2011 reported a 28.3% increase in cannabis exposures in decriminalised states, compared to non-legal states. These studies also highlight the risk of paediatric cannabis exposures. Increased use of cannabis by family members, increased likelihood of oral ingestion, and increased

potency of products, are likely the reason for this increase. Caregivers are also more likely to report cases in areas where cannabis is decriminalised.[19]

A 2013 study described the distribution of calls to the Tygerberg Poison Information Centre over one year. In this study, medicine exposures formed 35.2% of total calls. The Drugs of Abuse category featured 0 recorded cases. Other common exposures reported are non-drug chemicals (52.7%) and biological toxins (12.6%).[20] The Tygerberg Poison Information Centre was established in 1977 and is based at the University of Stellenbosch in the Western Cape, a province in South Africa. This service is provided in conjunction with the Poisons Information Centre at the Red Cross Children's Hospital. It provides a 24/7 telephonic service to health professionals and the public under the banner of the Poisons Information Helpline of the Western Cape (PIHWC).

Cannabis is considered a benign drug, and although many exposures are considered mild, serious intoxication can occur. The toxic effects of cannabis can be divided into neuropsychiatric and physical effects. Acute intoxication can lead to impaired coordination and perception, agitation and anxiety, and acute psychotic symptoms like hallucination and paranoia. Cannabis use can also precipitate substance induced psychosis. It has been shown to increase rates of admission in patients with schizophrenia and can trigger manic episodes in patients with Bipolar Mood Disorder.[2,3] A retrospective chart review in Colorado found neuropsychiatric presentations to be the third most common (24.7%) reason for cannabis-related emergency department presentations. In this subgroup, acute psychiatric symptoms (46%) and acute exacerbation of known psychiatric disorder (14.1%) was the most common. [21] Gastrointestinal and cardiovascular symptoms are also commonly reported after cannabis exposure. The same retrospective chart review reported a 30.7% incidence of gastrointestinal symptoms, and Cannabinoid Hyperemesis Syndrome (CHS) was reported in 17% of cases. [21] CHS is a syndrome marked by episodes of cyclical vomiting and abdominal pain in the

setting of chronic cannabis use. The pathophysiology is poorly understood but is probably due to the down regulation of CB1 receptors in the gut associated with long term THC exposure.[22] Cardiovascular symptoms include tachycardia, orthostatic hypotension, and syncope as well as major cardiac events. The risk for a major acute cardiac event is 5 times higher in cannabis users.[2,3] Although cases of acute myocardial infarction have been reported, the Colorado study indicates that cardiovascular symptoms (3.6%) are not common. Compared to the Colorado study, a review of the Alaska and Oregon Poison Centre database reported a much higher incidence of neurological symptoms (80.6%) followed by gastrointestinal symptoms (26.5%) and cardiovascular symptoms (14.6%).[23] It is important to note that these symptoms do not occur in isolation nor are they consistent in their severity. Acute cannabis exposure and intoxication can present with a range of symptoms and be influenced by many factors, including the route of exposure, the quantity taken, the THC content, age, as well as the presence of any co-ingested substances.

The route of exposure, whether inhaled or ingested, plays a major role in the presentation of cannabis intoxication. The Colorado review reported inhaled cannabis exposure (90.2%) to be more common than edible cannabis exposure (8.8%).[21] It also reported inhaled cannabis exposure (32.3%) to cause gastrointestinal symptoms twice as often as edible exposures (15.1%). However, the Alaska and Oregon Poison Centre reported exposure to edible cannabis products (73.9%) to be far more common than inhaled cannabis products (22.5%), and cannabis ingestion exposures were present in 90.1% of cases reported with neurological symptoms.[23] Edible forms of cannabis can present with worse symptoms of intoxication, most notably neurological and cardiovascular symptoms. Compared to inhalation, edibles have a delayed onset (peaking at 3 hours), and due to erratic and slow absorption, have a longer duration of action (up to 12 hours).[2,3] This can result in delayed plasma peak concentrations and possible ingestion of repeat doses leading to a compounding toxic effect.

It is unclear why poison centres have a higher incidence of edible exposures. A possible reason may be the anonymity provided by the poison centre. The selling of edible products in South Africa is illegal, and most products are homemade which causes a variable effect as dosing and THC content cannot be guaranteed.

Most paediatric cannabis exposures occur after accidental oral ingestion. A study conducted from 2005 to 2015 in Colorado found that unintentional oral cannabis exposure was high in both emergency department (48%) and poison centre (74%) paediatric populations.[17] Products ingested by minors are commonly reported as infused edible products like cakes and candies, that can contain high levels of THC. Access is commonly from members of the household. A wide range of THC dosing in children has been reported. In a small cohort, 3.2mg/kg was associated with mild symptoms, and levels of 13mg/kg required ICU care.[24] Cannabis intoxication in children is commonly associated with neurological symptoms. A systematic review found common presenting symptoms to be lethargy (71%), ataxia (14%), hypotonia, mydriasis. Tachycardia and hypoventilation are also common presenting symptoms. In this systematic review, the paediatric intensive care admission rate was reported as 18%, with 6% of patients requiring intubation.[25]

The intrinsic toxic effects of cannabis are related to the amount of THC consumed, and variation in an individual's capability to metabolise THC. A dose of more than 7.5mg/m2 body surface area can lead to toxic effects.[26] Attempts to study the toxic effects from cannabis exposures in the public are severely hampered by uncertainty around the amount of cannabis consumed, and the THC content. Very few studies report accurate THC dosing, with many reporting unquantifiable amounts – 1 joint, 1 bite, or a fingertip. Cannabis is rarely used in isolation, and polysubstance use further confound the study of cannabis exposures. The review of the Drug Abuse Warning Network in the United States of America reported common co-ingested substances as alcohol (34%), stimulants like cocaine (44.1%), opiates

(26.9%) and sedatives like benzodiazepines (20.1%).[15] A retrospective review of ICD codes in Colorado amongst cannabis associated emergency department and urgent care visits reported adolescents co-ingested ethanol 4 times more compared to other drugs.[16] Although the type of co-ingested substances is commonly reported in the literature, the number of different compounds taken together, the amount taken, and what clinical effect can be attributed to them are not reliably reported.

While limited information has been gathered on the changes in cannabis presentations internationally, no studies are reporting the situation in South Africa. Gathering data on cannabis usage by the general population is extremely difficult and subject to major ethical considerations. Thus, we are left with either using data from emergency departments or poison centres. Poison centres are a valuable resource to emergency departments and the public at large for reporting toxicological emergencies. They act as an accessible source of accurate treatment guidance in the event of a toxicological emergency and have a cost-saving benefit by triaging low-level toxicologic events away from presenting to the emergency department. They also assist with health surveillance in evolving trends in toxicological presentations.[27] Thanks to the excellent records kept by the PIHWC, this is a resource that can be looked at to answer the research question.

Therefore, our study aims to gain insight into cannabis exposures and usage by describing the characteristics of all reports made to a national poison centre that relate to cannabis exposure and how they have changed over the past 4 years.

Study Objectives

The primary objectives are as follows:

1. To describe the demographics of reported cases related to cannabis-adverse events.
2. To describe the characteristics of reported cases of cannabis-adverse events

3. To describe the type of cannabis used

4. To describe changes in reports on cannabis-adverse events over the four-year period.

The secondary objectives are as follows:

1.To describe the reason for taking cannabis

2. To compare single substance cannabis use with polysubstance cannabis use.

Methods and design

This will be a retrospective observational cross-sectional study. The study will conduct a secondary analysis of the AfriTox™ TeleLog Database (ATD) from the Poisons Information Helpline of the Western Cape (PIHWC). The PIHWC is located at the Poisons Information Centre Room 411, Institute of Child Health, Red Cross Children's Hospital, Klipfontein Road, Rondebosch, 7700 Cape Town, South Africa. The following URL - http://www.afritox.co.za/WhoWeAre.aspx can be accessed for more information on the PIHWC. The PIHWC allows 24/7 access for telephonic consultations related to acute poisonings by health care practitioners and the public. Although based in the Western Cape, this service is available nationally and to countries in the greater Southern African area. The ATD contains data for all calls made to the call centre from June 2015. The study sample will include all database entries that relate to cannabis use, made over the time 1 June 2015 to 30 June 2019. The study sample size will encompass approximately 80 calls, as per personal communication between the principal investigator and the head of the PIHWC. Verbal approval of the basis of the study has been obtained from the principal investigator before the completion of this protocol. The study sample will exclude all entries referencing non-humans, all calls originating outside South Africa, as well as any data entry where information has not been captured adequately. The study sample will be subcategorised into single substance cannabis use and polysubstance cannabis use.

A formal request for data will be made to the PIHWC to access the ATD once ethical requirements have been met. As per their data access policy, the PIHWC advisory board will review our application before granting access. The requested document is attached as appendix A. We will request a data series of all calls logged in the ATD, from 01 June 2015 to 30 June 2019 that refers to cannabis use. An example of the ATD data entry form is attached as appendix A. The complete list of variables that we will request from PHIWC is attached as appendix C.

Upon our successful request, the PIHWC will provide us with a specifically prepared excel data table. No data field that may contain identifiable information on patients call initiators or PIHWC staff will be included in our request. The data set will be password protected and access control limited to the principal investigator, supervisors, fellow research colleagues, and members of the ethics committee upon request. The resulting publication will comply with the STROBE guidelines for the publication of cross-sectional studies.

Data Analysis

Data analysis will be conducted in Excel and R Studio for R version 3.6.1 (2019-07-05). Categorical data will be described with frequencies and percentages. Parametric numbers will be described with means and standard deviations. Non-parametric numbers will be described with medians and inter-quartile range. Due to the low numbers, changes over the four years will be done using descriptive statistics only. If the numbers allow, then changes in demographic variables over the four years will be assessed using a one-way ANOVA for numerical values or Chi^2 or Fisher's exact test for categorical data.

Funding and Timing

The current budget for this research project is R1500 and will be carried by the principal investigator. The study will commence once ethical clearance has been obtained and will

continue until completion of the principal investigator registrar time, or until successful submission.

Ethics

An application will be made to the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for approval of research.

Problems

The Poison Centre has already been approached and given verbal approval for the project. Further limitations to consider is that the study sample may not adequately represent an emergency department population due to the difference in reporting of cannabis-adverse events, and a possible bias in documenting the reasons for cannabis use. Any other problems arising during the process of the study will be discussed with the study supervisor.

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Chapter 2: Research report

This research report is submitted for the degree: Master of Medicine (Emergency Medicine).

It is submitted in submissible format as an article for submission to an academic journal. The academic journal chosen for submission is the South African Medical Journal (SAMJ) and this research report follows the submission guidelines provided by the SAMJ

Title

An observational study of cannabis exposures reported to the Poison Information Helpline of the Western Cape.

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Author contributions

All authors contributed equally to the creation of this manuscript

Conflict of interest

The authors have no conflicts of interest to declare.

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Keywords

Emergency medicine, Cannabis, Toxicology, Paediatrics, Poison centre

Abstract

Background: Cannabis has gained popularity as a medicinal and recreational drug and has recently been decriminalised for private use in South Africa. Previous publications indicate an association between increased popularity and increased reports of cannabis exposures. We aim to study this association indirectly by conducting a secondary analysis of cannabis exposures reported to the Poison Information Helpline of the Western Cape in South Africa.

Objectives: To describe the demographics and characteristics of reported cannabis exposure cases from June 2015 to June 2019.

Methods: This was a retrospective, observational, cross-sectional study of reported cannabis exposures recorded in the AfriTox TeleLog Database. The following variables were collected: demographics; circumstances of exposure; route of exposure; symptom profile and management advice. Changes in reports made to the poison helpline from June 2015 to June 2019 were also noted as was the comparison between monosubstance exposure and polysubstance exposure.

Results: A total of 106 database entries were identified. Monosubstance use was reported in 70.8% of cases. Both genders were equally represented. The most common age groups were 20–59 years old (52.8%) followed by under 12 years old (27.3%). From June 2015 to June 2019 there was a 3 threefold increase in reported cases. Accidental overuse (40.6%), substance abuse (26.4%) and intentional self-harm (19.8%) were the most reported circumstances of exposure. The most common route of exposure was oral (66.0%) followed by inhalation (26.4%). Adverse effects are commonly reported after accidental versus non-accidental ($p<0.001$), oral ingestion versus inhaled ($p<0.001$) of monosubstance cannabis use. The most common symptoms reported were central nervous system-related (75.5%), followed by gastrointestinal symptoms (20.8%). Central nervous system involvement was

more commonly reported in children 12 years and younger (p=0.001) compared to those over 12 years.

Conclusion: We provide a South African perspective on the changes in cannabis exposures reported to the Poison Information Helpline of the Western Cape from June 2015 to June 2019. Monosubstance cannabis exposures, accidental exposures, and oral ingestions are more likely to lead to reports of undesired effects. Children 12 years and younger are more likely to report neurological symptoms.

Article

Background

In September 2018, South Africa joined many other countries with a landmark constitutional court ruling in favour of decriminalising cannabis for private cultivation and consumption.[1] The introduction of the Cannabis for Private Purposes Bill in 2020 further clarified how consumers can legally use cannabis. Despite being illegal, cannabis had been a popular drug in South Africa for many years.[2] Cannabis contains over 240 cannabinoid compounds, many of which have a physiological effect on endocannabinoid receptors. The main cannabinoid compounds contained in cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is responsible for a dose-related psychotropic effect, or the cannabis 'high'.[3] Cannabidiol, however, is commonly used for its health benefits. Health benefits include the treatment of chronic pain, nausea, vomiting, and weight loss in chronic disease.[4]

In May 2019, the South African Minister of Health amended the Medicines and Related Substance Act of 1965, excluding certain formulations of cannabidiol from the list of scheduled medicines. This exclusion provides guidelines regarding the levels of THC and cannabidiol contained in these formulations that do not require to be registered, as well as regulations regarding the health risks associated with its use.[5] Certain cannabis-based oils and other related health products are easily accessible to consumers without medical prescriptions. The actual concentration in many commercially available cannabis oil brands often differs from the declared content.[6]

The expectation is that changing legislation will lead to the increased use of cannabis products, but this has not been supported by recent international publications.[7,8] However, there has been an increase in reports of acute cannabis intoxication and other adverse effects made to health care facilities in countries where cannabis is legal.[9,10] Poison centres in the

same geographical area also documented an increase in the number of reported cannabis exposures, in both adult and paediatric populations.[11–13] Poison centres are an integral part of the health care system. They provide a cost-saving benefit and add value by triaging low risk and asymptomatic poison exposures away from emergency departments.[14] They also assist in public health surveillance by studying patterns of reported poisoning.[11,15]

In general, cannabis research is limited, and very little has been conducted in South Africa. There are obvious limitations in conducting such research. To gain some insight into the field, our study aimed to describe the demographics and characteristics of reported cannabis exposures over a 4-year period by reviewing national data captured by the Poisons Information Helpline of the Western Cape (PIHWC), South Africa

Methods

In this retrospective, observational, cross-sectional study, a secondary analysis of the AfriTox™ TeleLog Database (ATD) was conducted. This database is maintained by the Poisons Information Centre located in Room 411, Institute of Child Health, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700, Cape Town, South Africa. The PIHWC is a joint service provided by two poison centres, one located at Red Cross War Memorial Children's Hospital and the other at Tygerberg Hospital, Belville, and it provides a 24-hour telephonic consultation service assisting both health care practitioners and the public with poison-related consultation and information. For every case reported to the PIHWC, the following information is captured in the ATD: demographic data including age, gender and location, information regarding the circumstances of the exposure, the severity of the poisoning, recommendations, and advice. Poison exposure is categorised into 4 levels of severity using the Poisons Severity Score (PSS)[16]: 0 – No symptoms or signs related to poisoning, 1 – Mild, transient, or spontaneously resolving symptoms or signs, 2 –

Pronounced or prolonged symptoms or signs, 3 – Severe or life-threatening symptoms or signs. The PSS compares favourably to poison centre grading systems used in similar international studies.[11,12] We requested data entries captured over 4 years, from 1 June 2015, the inception date of the database, to 30 June 2019 that related to cannabis, dagga, marijuana, or any other derived name of cannabis. Ethics approval (M190904) was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, and our study complied with the STROBE guidelines for cross-sectional publications.[17]

Data analysis was conducted in Microsoft Excel (Office 365, version 2112, build 14729.202060, Microsoft, USA) and R Studio (RStudio Team (2019). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com). Categorical data is described using frequencies and percentages. Parametric and non-parametric numbers were determined by measure of skewness, and were described using means and standard deviations, and medians and interquartile ranges, respectively. To describe changes in demographic variables over time, we divided all data entries into four 12-month periods ranging from July to June of each year starting with June 2015. Changes in categorical data over time and between groups were assessed using the Chi-square test or Fisher's exact test. We considered a p-value of <0.05 to be significant.

Results

All database entries were reviewed for validity. Three double entries and two entries not related to cannabis use were removed. Where reports referenced more than one patient per entry, separate data entries were created for each patient. After review and removal of inaccurate data, there were a total of 106 entries, i.e., cases.

Monosubstance cannabis exposure accounted for 70.8% of reported cases, and the remainder were polysubstance cannabis exposures. The reported gender representation was almost

equal: males (50.9%), females (47.2%) and unidentified (1.9%). Ages ranged from 1 to 80 years, with a mean (SD) age of 23.4 (17.6) years. Most reports involved adults over the age of 20, while only 16.0% of reported cases involved adolescents between the ages of 13 and 19. Children 12 years and younger, with a median (IQR) age of 4 (3), were involved in 27.3% of reported cases. Significantly more cases of children aged 12 and younger reported adverse effects from monosubstance exposure compared to adults, who were more likely to report polysubstance exposure (Table 1)

Table 1: Reported cannabis exposure by age group.

Age group	Polysubstance	Monosubstance	Total	Fisher's exact test
Child (1-12)	1 (3.4%)	28 (96.5%)	29 (27.4%)	p =0.0002
Teen (13-19)	8 (47.1%)	9 (52.9%)	17 (16.0%)	p = 0.0888
Adult (>20)	22 (36.7%)	38 (63.3%)	60 (56.6%)	p = 0.0840
Total	31 (29.3%)	75 (70.8%)	106 (100%)	p < 0.0003

*Data reported as n (%)

There was a threefold increase in reported cases from June 2015 to June 2019. This increase was statistically significant compared to the total increase in cases reported to the PIHWC over the same period ($p < 0.001$) (Fig. 1A). Comparisons for monosubstance exposure to polysubstance exposure ($p = 0.9573$), and age groups ($p = 0.2922$) were not statistically significant over the same period (Fig 1B, C). Changes in gender over the period was statistically significant ($p = 0.0148$), due to an increase in males during the 2018/2019 period (Fig 1D).

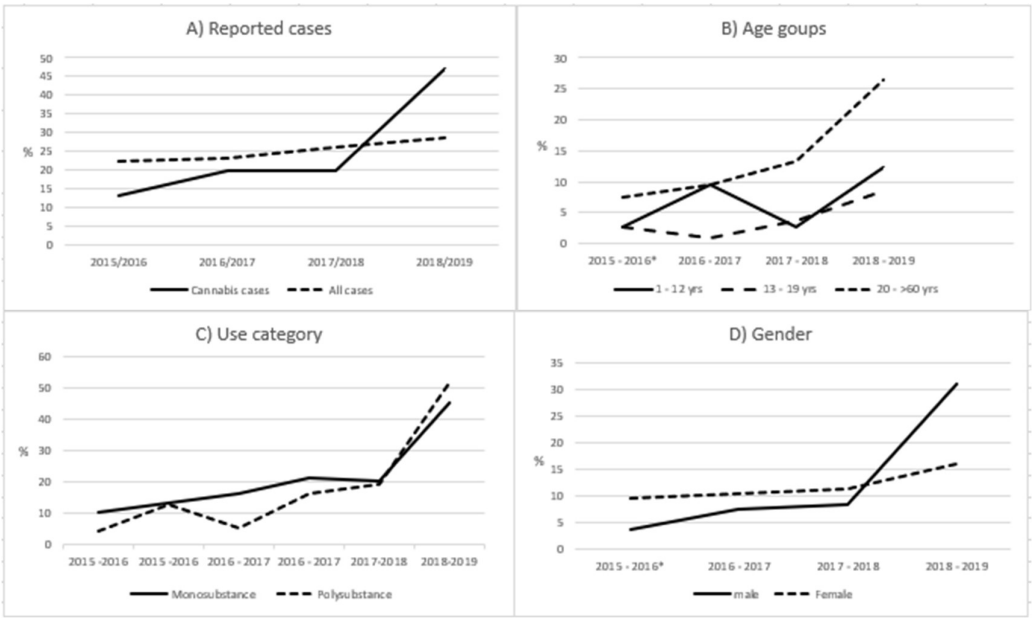

Figure 1: Changes in reported cannabis exposures by A) Reported cases, B) Age group, C) Use category and D) Gender.

Circumstances of exposure were reported as accidental (40.6%), substance abuse/misuse (26.4%), intentional self-harm (19.8%), malicious intent involving another person (4.7%), therapeutic error (4.7%) and unknown (3.8%). The circumstance of exposure was significantly different between monosubstance and polysubstance exposure ($p = 0.0003$,). Accidental exposure was more likely to occur in reports of monosubstance exposure, while intentional self-harm was more likely ($p < 0.0001$) to occur in reports of poly-substance exposure. (Fig. 2A) Accidental exposure and malicious exposure were significantly higher ($p < 0.0001$) in the age group, 12 and younger compared to other age groups. (Fig. 2B)

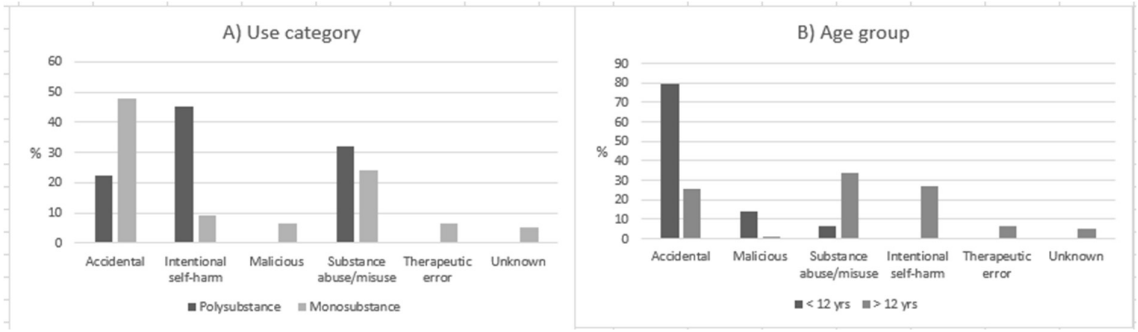

Figure 2: Comparison of circumstances of exposure according to A) Use category, and B) Age group

A Poison Severity Score (PSS) [16] category of 0 (1.9%) or 1 (75.5%) was recorded in most cases. A more severe PSS category of 3 (20.8%) or 4 (1.9%) was recorded in less than a quarter of cases. The PSS was not statistically different between monosubstance and polysubstance exposure groups (p = 0.8887) The PSS was statistically different for age groups (p = 0.0319) This is most likely due to a larger percentage of category 3 exposure in under 12-year-olds (20,7%) compared to over 12-year-olds (2.59)

Symptoms recorded by the PIHWC were categorised into central nervous system symptoms (the most common category), followed by gastrointestinal and cardiovascular symptoms. (Table 2) Symptom category was not statistically different between the mono-substance group and poly-substance group (p=0.287). Symptom category was statistically different between age groups (p = 0.0005) due to the high incidence of central nervous system symptoms reported in cases of under 12-year-olds. Neuro-depression was most common in this age group (75.9%), compared to over 12-year-olds where neuro-excitation was the most common central nervous system symptom (66.7%). (Table 2)

Table 2: Symptoms reported by use category and age group

Symptoms	Monosubstance	Polysubstance	p-value	< 12 yrs.	> 12 yrs.	p-value	Total
CNS symptoms	58 (77,33)	22 (70.97)	0.148	29 (100)	51 (66.23)	0.0001	80 (75.47)
Neuro-depression	30 (51.72)	8 (36.36)		22 (75.86)	16 (31.37)		38 (47.5)
Neuro-excitation	28 (48.28)	13 (59.09)		7 (24.14)	34 (66.67)		41 (51.25)
Seizure	0 (0)	1 (4.55)		0 (0)	1 (1.96)		1 (1.25)
GIT symptoms	17 (22.67)	5 (16.13)	0.395	3 (10.34)	19 (24.68)	0.659	22 (20.75)
Nausea	5 (29.41)	0 (0)		0 (0)	5 (26.32)		5 (22.73)
Vomiting	10 (58.82)	5 (100)		3 (100)	12 (63.16)		15 (68.18)
Abdominal pain	2 (11.76)	0 (0)		0 (0)	2 (10.53)		2 (9.09)
CVS symptoms	15 (20)	5 (16.13)	0.185	1 (3.45)	19 (24.68)	0.55	20 (18.87)
Chest pain	1 (6.67)	1 (20)		0 (0)	2 (10.53)		2 (10)
Hypotension	0 (0)	1 (20)		0 (0)	1 (5.26)		1 (5)
Palpitations	8 (53.33)	1 (20)		0 (0)	9 (47.37)		9 (45)
Tachycardia	6 (40)	2 (40)		1 (100)	7 (36.84)		8 (40)
Total	75 (70.75)	31 (29.24)	0.287	29 (27.35)	77 (72.64)	0.0005	106 (100)

*Data reported as n (%)
**CNS – Central nervous system, GIT – Gastrointestinal, CVS – cardiovascular system.

Routes of exposure were most recorded as oral ingestion (66.0%) followed by inhalation (26.4%). A review of the available data found that cannabis was commonly ingested in the form of edible products (48.6%) or oil-based products (45.7%). Monosubstance exposure mostly occurred due to oral ingestion (Fig 3A), while in case reports of polysubstance exposure, cannabis use was significantly more likely to be inhaled ($p<0.0001$). Reported substances commonly ingested in combination with cannabis were cocaine (48.3%) opioids (38.7%), sedatives (32.2%) and alcohol (22.6%).

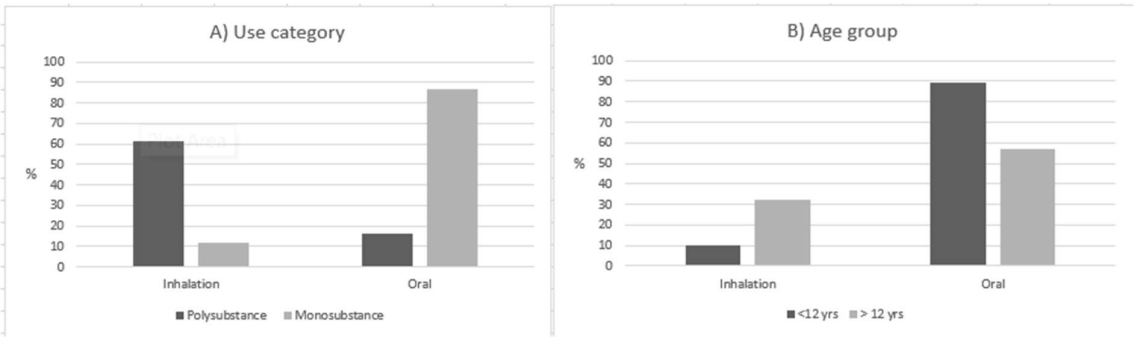

Figure 3: Comparison of route of exposure by A) Use category, and B) Age group.

The oral route of exposure was also statistically more common in the age group 12 and younger compared to those older than 12 years ($p = 0.0046$). (Fig. 3B) Ingestion of food-based cannabis products were commonly reported in children aged 12 and younger (62.1%). These food-based products were mostly homemade cookies, muffins or scrambled eggs mixed with cannabis. More than one subject per case was reported in 17,0% of cases. Case reports involving children 12 years and younger were more likely to involve more than one subject (44.8%), compared to the rest of the dataset (6.5%). This difference was statistically significant ($p < 0.0001$).

Most cases were reported by medical personnel (84.9%) outside of normal office hours (77.4%). Most cases were reported from hospital facilities (67.0%) followed by non-hospital facilities (17.0%). In most cases, the PIHWC advised observation in a hospital (64.2%). We were not able to report on the amount of cannabis used, nor the concentration of THC or cannabidiol as this information was not reliably recorded in the Afritox Telelog Database.

Discussion

In our review of cannabis exposures recorded by the PIHWC, there was a substantial increase in the number of cases reported from 1 June 2015 to 31 June 2019, especially in males. More reports were made concerning cannabis exposure alone compared to cannabis exposure in combination with other substances. In monosubstance exposure, cannabis was more likely to be ingested accidentally by the oral route, whereas in polysubstance exposure reports, cannabis was more likely to be smoked intentionally. Accidental ingestion of edible cannabis products was a common occurrence in patients aged 12 years and younger. The most common presenting symptoms were central nervous system symptoms, mostly reported as either neuro-depression or neuro-excitation. Children aged 12 and younger were significantly

more likely to present with neuro-depression and was statistically more likely to have a more severe PSS.

A previous review of poison centre data in South Africa in 2013 did not report specifically on cannabis exposure. [15] Our review shows an increase in cases reported to the PIHWC from June 2015 to June 2019. Our dataset also indicates an above-average increase in reported cases in 2018/2019. This coincides with the constitutional court verdict decriminalising cannabis for private use. [1] An association between the legalisation of cannabis and increased reports of cannabis exposure to poison centres has been shown in the United States of America (30-79%).[11,12,18,19] Possible reasons for the rising number of reports associated with a change in legal status are an increase in popularity and a decrease in negative health connotations. The easing of legal restrictions may also lead to less reluctance amongst cannabis users to report exposure and subsequent undesirable effects.[20] To further investigate the significance of the increasing number of reports of adverse effects due to cannabis exposure and its association with decriminalisation, a comparison with other departments involved in acute patient care is needed, as not all cases may be reported to the poison centre.

We found most cases reported monosubstance exposure, with a Poison Severity Score of 0 or 1. Similarly, a review of cannabis exposures reported to the Israeli Poison Information Centre found mono-substance exposure in up to 83,5% of reported cases, with a no/minor severity recorded in 71.9%.[13] We found that polysubstance exposure reports were more likely to involve adults intentionally exposed to inhaled cannabis products. Stimulants like cocaine, sedatives and opioids are commonly co-ingested in reported cannabis exposure, [9,10] and our findings are similar.

In a previous study of patients presenting to the emergency department in Aurora, Colorado, gastrointestinal symptoms and exacerbation of psychiatric symptoms were commonly associated with cannabis exposure.[21] In contrast to this, most cannabis-related exposures reported to the PIHWC had neurological symptoms with varying levels of neuro-depression or neuro-excitation as part of the main complaint. Gastrointestinal and cardiovascular symptoms were also reported but were less common when compared to neurological symptoms. A study conducted at the Alaska/Oregon Poison Centre by Noble et al. shows a similar propensity of neurological symptoms (80.6%) compared to gastrointestinal symptoms (26.5%) and cardiovascular symptoms (14.6%). [22] The Israeli Poison Information Centre review also found a high incidence of neurological symptoms (60%).[13] Neurological symptoms after cannabis exposure are concerning and signifies more severe poisoning and increased concern amongst users. This may explain the increased number of reports made to the PIHWC

We found that neurological symptoms, in particular neuro-depression, to be the most common symptoms in children reported to the PIHWC. Similarly, the Alaska/Oregon Poison Centre study found neurological (69%) and specifically neuro-depression (52%) commonly reported in paediatric cannabis exposure.[22] This finding is not isolated to poison centre reviews, as a systematic review of unintentional paediatric cannabis exposure found neurological symptoms like lethargy, ataxia, hypotonia and mydriasis to be the most common findings. [23] Both worsening neurological symptoms and younger age may lead caregivers to be more likely to report exposure in children to the PIHWC.

When cannabis is consumed orally it is more potent, with delayed and erratic absorption compared to inhaled cannabis.[3] It is more likely to present with adverse effects like neurological and psychiatric symptoms, whereas inhaled cannabis is more likely to cause

gastrointestinal symptoms like cannabis hyperemesis syndrome.[24] In our review, oral ingestion of cannabis was the most common route of exposure. Similarly, the Alaska/Oregon Poison Centre review reported edible cannabis exposure in up to 56.9% of cases.[22] High rates of oral exposure may contribute to the increased number of cases with neurological symptoms reported to the PIHWC.

We found edible and oil-based products to be the most ingested form of cannabis. More than half of confirmed edible exposures occurred in children aged 12 and younger. The Alaska/Oregon Poison Centre review reported edible exposure in 67% of children aged 12 and younger. [22] Similarly, a study in Colorado showed a 74% exposure rate to edible cannabis products reported to the regional poison centre amongst paediatric patients.[12] Edible cannabis poses a novel risk to paediatric populations, who may ingest cannabis edibles like sweets or baked goods or cannabis resin that looks like chocolate.[23] This may further contribute to the high incidence of neurological symptoms reported in children 12 years and younger.[17]

Most of our cases were reported after-hours, by medical professionals from a health care facility. Similarly, the Oregon/Alaska Poison Centre review found 54% of calls originated from an emergency department,[22] while the Israeli Poison Information Centre reported only 23% of calls were made by the public.[13] Although cannabis intoxication is considered mild it is still capable of producing symptoms of intoxication, leading to health care contact.[13,25] This may signify that people who require health care assistance from cannabis exposure do so as a matter of urgency. Accidental and unintentional exposure to cannabis, especially in the age group 12 years and younger, is commonly found in our dataset. Studies done in Colorado,[11,12] Alaska and Oregon[22] had similar findings. Many cases reported of children 12 years and younger, involved more than one child. This is likely due to imitative behaviour

found in paediatric poison ingestions[26] which may further influence health-seeking behaviour.

The design of our study introduced various limitations, however, studies in this field are ethically challenging. Our sample size was small compared to other similar studies and might not be an adequate representation of the current situation in South Africa. A secondary review of an existing database has inherent limitations and risks introducing confounding, measurement, and selection bias. The use of poison centre data also has limitations, as only those cases reported to the PIHWC could be included. Awareness of the poison information helpline as a resource; accessibility to other resources; the safety profile of cannabis and an uncertain legal environment can all influence the study sample in terms of quantity and severity. Compared to other studies,[22] data was collected using methods not specifically tailored towards our study objectives. We were unable to confidently report on the amount and strength of cannabis used, because cases were commonly reported with unquantifiable amounts like one joint, half a cookie, or a fingertip. Difficulty in establishing the content and concentration of homemade cannabis products, and quantifying the amount used is an ongoing problem in research around this subject.[22] This shortcoming will not be addressed unless adequate regulation of cannabis products exists. Differences in socio-economic, legal and population demographics make it difficult to draw comparisons with similar studies conducted in other countries and their findings may not apply to the South African setting.

Conclusion

Our investigation provides a South African perspective of the adverse effects of cannabis exposure as reported to the Poisons Information Helpline of the Western Cape, and how it has changed over a 4-year period. As more health benefits from cannabis are reported, so too will its social acceptability increase and along with that the rate of adverse effects. Our data

highlights the vulnerability of children under 12 years of age accidentally ingesting cannabis who are especially at risk of developing neurological symptoms. Cannabis use is not without consequences, and it is important for all health care practitioners involved in acute patient care to be aware of the various adverse effects associated with its use. Further research is needed in other areas such as emergency departments as well as the general population to understand the impact of cannabis-related adverse effects in South Africa.

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Chapter 3: Submission requirements (SAMJ)

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g., 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g., 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g., '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g., µ not u for micro, a not for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e., 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g., TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g., '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature

- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counsellors. J Genet Counsel 2008; 17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results, and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion, and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g., primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social, or cultural factors (e.g., smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g., what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g., '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g., 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g., *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e., not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others. [3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between {}.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

• Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

• Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

• Acts:

South Africa. National Health Act No. 61 of 2003.

• Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

• Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

• Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

• Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no. after the v

- *Other references (e.g., reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g., '... (Prof. Michael Jones, personal communication)'.

Western Cape Government
Health

Poisons Information Helpline of the Western Cape (PIHWC)
AfriTox™ TeleLog Database

AfriTox TeleLog

Enquiries to: Dr Cindy Stephen
Telephone: +27 (21) 658 5308 Email: cindy.stephen@uct.ac.za

Application to use data from the AfriTox TeleLog database

This form is to be used when requesting use of data from the PIHWC AfriTox TeleLog database for research purposes.

- *Please send a signed copy of this form with a brief outline of your research protocol (template overleaf) to Dr Cindy Stephen (address above).*
- *Once approval is granted, and the final proposal with relevant ethics approval has been received by the PIHWC Advisory Committee, the requested data will be provided in consultation with Dr Stephen.*
- *The AfriTox TeleLog database is registered with the University of Cape Town's Faculty of Health Science Human Research Ethics Committee (R014/2014). This does not preclude you from obtaining the usual ethics approval for your specific study.*

Surname: Venter	Name: Jakus	Title: Dr
Address: Division of Emergency Medicine, School of Medicine, University of the Witwatersrand, York Road, Parktown, Johannesburg, Gauteng, South Africa		Email:jakus.venter@gmail.com
		Cell: 079 714 0528
Current employer:	Gauteng Department of Health	
Current academic affiliation:	Division of Emergency Medicine, University of Witwatersrand	
Study purpose:	Degree ☑	Other ☐
	Publication ☐	Conference ☐
Type of study:	Descriptive ☐	Analytical ☐
Data levels:	Province(s): Gauteng, Limpopo, Mpumalanga, North-West, Northern Cape, Western Cape, Eastern Cape, Kwazulu Natal, Free state	
	District(s):	
	Hospital(s):	
Data format requested:	Full use of the AfriTox TeleLog database to generate queries	Specifically prepared Excel data tables

Declaration of intent:

1. I declare that the data will be used solely for the purpose outlined above, and that absolute confidentiality will be maintained at all times. No patient identifiers will be sought nor used in my research.
2. I will acknowledge the PIHWC AfriTox TeleLog database as my data source, where TeleLog data are used as follows: Poisons Information Helpline of the Western Cape (PIHWC), AfriTox™ TeleLog Database
3. Prior to publication or submission of any work arising out of this study, I undertake to submit an electronic version of the publication(s) to the PIHWC Advisory Committee for final review.

Name: Dr Jakus Venter	Signature:	Date: 27/07/2019

Approval on behalf of the PIHWC Advisory Committee

Full use of the AfriTox TeleLog database to generate queries	Specifically prepared Excel data tables

Name: C.R. STEPHEN	Signature:	Date: 12.08.2019

Protocol Outline

(Please write one or two sentences only, under each heading)

Title of study

Reports of cannabis adverse-events to a national poison center: an observational study

Area of research interest

Toxicology, Emergency Medicine, Health seeking behaviour

Research 'Problem Statement' and Question

With the increase in cannabis popularity and recent legalisation, is there a change in demographics of patients that requires emergency healthcare assistance for cannabis adverse-events

Aims and objectives

The aim is to provide insight into the patient population that requires emergency healthcare assistance for cannabis adverse-effects by analysing data captured by the Poisons Information Helpline of the Western Cape

The primary objectives are as follows:

1. To describe the demographics of reported cases related to cannabis-adverse events
2. To describe the characteristics of reported cases of cannabis-adverse events
3. To describe the type of cannabis used
4. To describe changes in reports on cannabis-adverse events over the four year period.

The secondary objectives are as follows:

1.To describe the reason for taking cannabis

2. To compare single substance cannabis use with polysubstance cannabis use

Study design

This is a retrospective observational cross-sectional study

Setting

This is a secondary analysis of existing database

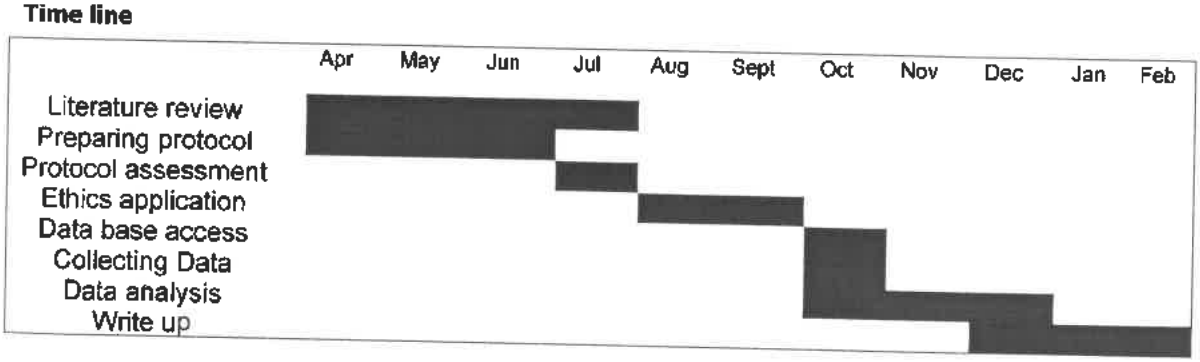
Data analysis

Data analysis will be conducted in Excel and SAS/In Graph.
Categorical data will be described with frequencies and percentages. Parametric numbers will be described with means and standard deviations. Non-parametric numbers will be described with medians and inter-quartile range. Due to the low numbers, changes over the four years will be done using descriptive statistics only. If the numbers allow, then changes in demographic variables over the four years will be assessed using a one-way ANOVA for numerical values or Chi^2 for categorical data.

Ethical consideration

An application will be made to the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for approval of research

Time line



Co-workers

Name	Affiliation	email
Dr Sashen Murugan	Wits	Sashen.murugan@gmail.com
Dr Alison Bentley	Wits	dralisonbentley@gmail.com

Key stakeholders

Division of Emergency Medicine, University of Witwatersrand

References

1. The constitutional Court of South Africa. September 2018. Minister of Justice and Constitutional Development and others V Prince CCT108/17. Available: https://www.concourt.org.za/index.php/judgement/260-minister-of-justice-and-constitutional-development-and-others-v-prince-cct108-17 [Accessed 20.01.2019]
2. South Africa. Dept. of Health. 2019. The Medicines and Related Substances Act, 1965 (Act No. 101 of 1965). Exclusion of certain preparations containing cannabidiol (CBD) from operation of certain provisions of the medicines and related substances Act, 1965(Act No. 101 of 1965). Government Gazette No. 10949:42477 23 May
3. Sagy I, Peleg-Sagy T, Barski L, et al. 2018. Ethical issues in medical cannabis use. *European Journal of Internal Medicine.* 49:20-22. doi: 10.1016/j.ejim.2018.01.016
4. Schindlers Attorneys. 25.10.2018. A legal breakdown of the current situation on Cannabis in South Africa. Available: https://medicalcannabis.co.za/2018/10/a-legal-breakdown-of-the-current-situation-on-cannabis-in-south-africa/ [Accessed 23.05.2019]
5. Whiting PF, Wolff RF, Deshpande S, et al. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of the American Medical Association.* 313(24):2456-2473. doi: 10.1001/jama.2015.6358
6. Volkow ND, Baler R. 2019. Emergency Department Visits From Edible Versus Inhalable Cannabis. *Annals of Internal Medicine.* 170(8):569. doi: 10.7326/M19-0542.
7. Wang GS, le Lait M-C, Deakyne SJ, et al. 2016. Unintentional Paediatric Exposures to Marijuana in Colorado, 2009-2015. *JAMA Paediatrics.* 170(9):e160971. doi: 10.1001/jamapediatrics.2016.0971
8. Tak CR, Malheiro MC, Bennett HKW, Crouch BI. 2017. The value of a poison control center in preventing unnecessary ED visits and hospital charges: A multi-year analysis. *The American Journal of Emergency Medicine.* 35(3):438-443. doi: 10.1016/j.ajem.2016.11.049
9. Veale DJH, Wium CA, Müller GJ. 2013. Toxicovigilance I: A survey of acute poisonings in South Africa based on Tygerberg Poison Information centre data. *South African Medical Journal.* 103(5)293-7. doi: 10.7196/SAMJ.6647
10. Kim HS, Monte AA. 2016. Colorado Cannabis Legalization and Its Effect on Emergency Care. *Annals of Emergency Medicine.* 68(1)71-5. doi: 10.1016/j.annemergmed.2016.01.004

List of variables to request from Poison Information Helpline of the Western Cape (PIHWC)

1) Call Date
2) Category of call
3) Patient related
4) Category of Caller
5) Country of Origin
6) SA Province
7) Sex
8) Age (Y/M/D)
9) Substance Name
10) AfriTox Name
11) Group
12) Use Category
13) Specific Use
14) Amount
15) Toxic Dose
16) Route
17) Circumstance of Poisoning
18) Place of Poisoning
19) Poisoning severity score
20) Clinical Details
21) Course of Action Advised
22) Additional Treatment Advised
23) Follow Up Notes

Poisons Information Helpline: AfriTox TeleLog© Data Entry Form

Call Date				
Call Time Start		Call Time End		*Duration (computer generated)*

Call ID No.	*(computer generated)*	
SPI Name		
Category of Call	Patient related	
	General	☐ Checking tel no. ☐ Forensic ☐ Media ☐ Poison info ☐Other
	Non-PIH	☐ Drug Info ☐ Medical Info ☐Other

CALLER| LOCATION	Caller Name			
	Phone number			
	Category of Caller	☐ Public	*Relationship*	Self | Parent | Other family | None | Unknown
		☐ Medical pers.	*Facility type*	Doctor | EMRS | Clinic | Pharmacy | Vet | Unknown
	Facility name	*(drop down list)*		
	Country of Origin	☐ SA	☐ Outside SA	
	City			
	SA Province	*(drop down list)*		
	District	*(drop down list)*		

PATIENT	Human/Animal	☐ Human ☐ Animal *(drop down list)*		
	Patient Name			
	Sex	☐ M ☐ F ☐ Unknown		
		If Female	☐ Pregnant ☐ Lactating	
	DOB			
	Age (Y/M/D)	|Years| |Months| |Days| *(computer generated)*		
		Age group (computer generated)	<1 yrs / 1-<2yrs / 2-<3yrs / 3-<4yrs / 4-<5yrs / 5-<6yrs / 6-12yrs / 13-19yrs / 20-59 yrs / ≥60 yrs	
	Weight (kg)		Suggested	*(computer generated)*
	Repeat call	☐ Yes ☐ No		

SUBSTANCE	Substance Name	
	AfriTox Name	
	Manufacturer	
	Group	☐ Single ☐ Mixture ☐ Toxic Group ☐ Unknown
	Use Category	Specific Use
	Agri (Herb, Fungicide, Other)	*Adjuvants, plant growth regulators | Fertilisers, trace elements | Fungicides | Herbicides, weed killers | Unknown agri products (herb/fungi/other)*
	Animal bites, stings	*Bee or wasp sting | Insect bite/sting (excluding wasps, bees, spiders) | Marine sting | Other bite/sting | Scorpion sting | Snake bite | Spider bite | Unknown bite/sting*
	Antiseptics	*Environmental antiseptics | Skin or wound antiseptics | Unknown antiseptics*
	Cosmetics	*Bath or shower soap products | Dental products including toothpaste| Deodorants & Antiperspirants | Depilatory products | Facial cleansers, toners, masks | Hair dyes, bleaches, straighteners | Hair shampoo, conditioner, dressing | Make-up | Moisturisers & sunscreens for face or body | Nail products | Perfumes and aftershave | Powder, talc | Shaving products excl aftershave | Skin lightener | Unknown cosmetics*

Food	*Alcoholic beverages | Food additives | Food poisoning | Unknown foods*
Handyman	*Detergents for industrial or handyman use | Dye - leather, clothes, shoes| Firelighters, fuels | Glues, sealants, fillers, putty | Oils and lubricants | Other handyman products | Paint thinners, stripper | Paints, varnishes, glazes | Paraffin | Unknown handyman products | Writing materials*
Household	*Bleach | Descalers, sterilisers, stain removers | Detergents for dish washing and laundry | Dish rinsing aids | Drain cleaners | Fabric softeners | General household cleansing agents | Hand cleaners | Household fragrances & deodorisers | Other household agents | Oven cleaners | Polishes - floor, furniture, car, shoe | Polishes - metal | Swimming pool products | Unknown household agents*
Industrial	*Aerosol propellants, refrigerants | Anti-freeze | Batteries & their ingredients | Carbon monoxide, exhaust fumes / Cement, adhesives and fillers | Desiccant | Ice bricks & freezer pack fillers | Mercury, lead & heavy metals | Other industrial products | Petroleum products, solvents | Photographic developers, fixers, etc. | Tear gas & riot control agents | Unknown industrial products*
Insecticides & Rodenticides	*Animal repellents | Insect and moth repellents | Insect attractants | Insecticides | Rodenticides | Unknown insecticides/rodenticides*
Pharmaceuticals	*Analgesics/anaesthetics & antipyretics | Antacids & ulcer remedies | Anthelmintics | Anti-infectives | Anticoagulants | Anticonvulsants | Antidiarrhoeal agents | Anti-emetics | Antirheumatics & gout agents | Antispasmodics for GIT & GUT | Bronchodilators | Cardiovascular medicines | Cold & flu remedies, antihistamines | Cough mixtures | Cytotoxics | Hormones & hypoglycaemic agents |Laxatives | Lipid-lowering agents | Other drugs | Psychiatric & neurological medicines | Skeletal muscle relaxants | Sleeping pills | Slimming preparations | Topicals (creams, drops, oral preps) | Traditional medicines | Unknown drugs | Vitamins, tonics, minerals*
Plants and Fungi	*Flower, leaf, bark, stem | Fruit, berry, seed/pip | Fungi, mushrooms | Root, bulb | Sap | Unknown plants*
Unknown	*Unknown*
Amount	
Toxic Dose	☐ Yes ☐ No ☐ Unknown
Route	Oral Bite, sting Inhalation Inj IM Inj IV Inj SC Ocular Otic Mucosal Placental Rectal Skin Unknown

CLINICAL	Circumstances of poisoning	Accidental | Contamination | Intentional self-harm | Malicious | Substance abuse | Therapeutic error | Unknown
	Place of poisoning	Home |Healthcare Facility |School | Workplace |Other
	Interval since exposure *(in hours)*	
	Poisoning severity score	0 | 1 | 2 | 3 | 4 | Unknown
	Clinical Details	

ADVICE|COMMENT	Course of Action Advised	No treatment Observe at home First aid Take to doctor/hospital Observe in hospital Activated charcoal Transfer to other medical facility Other
	Additional Treatment Advised	
	Comment	

FOLLOW UP NOTES	Follow up Notes

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Jakobus Kritzinger Venter

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190904 MED19-09-010

NAME: (Principal Investigator)	Dr Jakobus Kritzinger Venter
DEPARTMENT:	Division of Emergency Medicine
PROJECT TITLE:	Reports of cannabis adverse-events to a national poison center: an observational study
DATE CONSIDERED:	27/09/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Sashen Murugan and Dr Alison Bentley

APPROVED BY: Dr C Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 08/11/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

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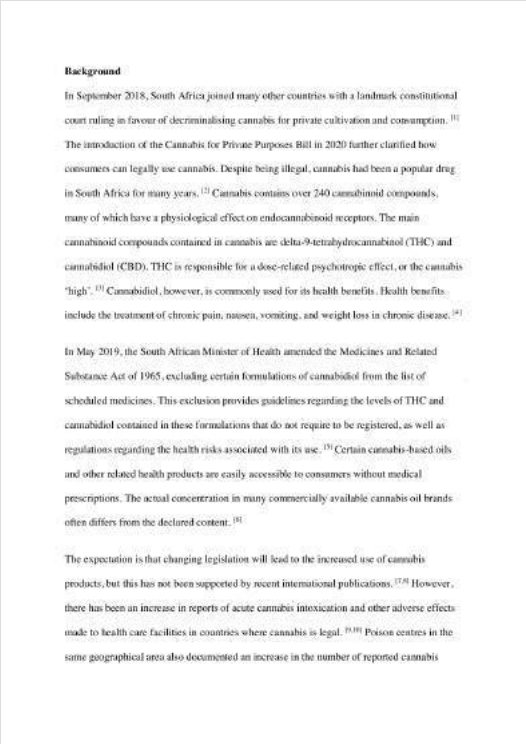

Background

In September 2018, South Africa joined many other countries with a landmark constitutional court ruling in favour of decriminalising cannabis for private cultivation and consumption. [1] The introduction of the Cannabis for Private Purposes Bill in 2020 further clarified how consumers can legally use cannabis. Despite being illegal, cannabis had been a popular drug in South Africa for many years. [2] Cannabis contains over 240 cannabinoid compounds, many of which have a physiological effect on endocannabinoid receptors. The main cannabinoid compounds contained in cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is responsible for a dose-related psychotropic effect, or the cannabis "high". [3] Cannabidiol, however, is commonly used for its health benefits. Health benefits include the treatment of chronic pain, nausea, vomiting, and weight loss in chronic disease. [4]

In May 2019, the South African Minister of Health amended the Medicines and Related Substance Act of 1965, excluding certain formulations of cannabidiol from the list of scheduled medicines. This exclusion provides guidelines regarding the levels of THC and cannabidiol contained in these formulations that do not require to be registered, as well as regulations regarding the health risks associated with its use. [5] Certain cannabis-based oils and other related health products are easily accessible to consumers without medical prescriptions. The actual concentration in many commercially available cannabis oil brands often differs from the declared content. [6]

The expectation is that changing legislation will lead to the increased use of cannabis products, but this has not been supported by recent international publications. [7,8] However, there has been an increase in reports of acute cannabis intoxication and other adverse effects made to health care facilities in countries where cannabis is legal. [9,10] Poison centres in the same geographical area also documented an increase in the number of reported cannabis

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"36th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 24-27 May, 2016, Madrid, Spain", Clinical Toxicology, 2016 Publication	1%
2	www.tandfonline.com Internet Source	1%
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Epithelial Dysplasia", Journal of Clinical Medicine, 2021
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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

APPLICATION FOR CHANGE OF TITLE OF APPROVED RESEARCH REPORT, DISSERTATION OR THESIS

Student Surname and Initials: Venter J K Student Number: 1984325

Degree: MMed Emergency Medicine Department: Emergency Medicine

Telephone: 079 714 0528 E-mail: jakus.venter@gmail.com

Current Title: Reports of cannabis adverse-events to a national poison centre: an observational study.

New Title: An observational study of cannabis exposures reported to the Poison Information Helpline of the Western Cape

Motivation / Reason for title change:

The title change has been suggested by Dr Cindy Stephen, a representative of the Red Cross War Memorial Children's Hospital Poisons Informations Centre and the Poisons Information Helpline of the Western Cape. Our study aims to describe the toxicological characteristics of cannabis use, an unregulated substance. We would like to title of our study to better reflect this. The term adverse events is used to describe unwanted effects from pharmaceutical substances. In toxicology, the term exposure is more appropriate to describe patient interactions with an unregulated substances.

Approvals / signatures:

Student Signature: Date: 14/12/2021

Supervisor 1 – Name & Surname: Dr Sashen Murugan

Department: Department of Emergency Medicine

Supervisor Telephone: 081 049 9318 Supervisor E-mail: sashen.murugan@gmail.com

Supervisor Signature: Date: 14/12/2020

1

Supervisor 2 – Name & Surname: Dr Alison Bentley

Department: Department of Emergency Medicine

Supervisor Telephone: 074 236 3087 Supervisor E-mail: dralisonbentley@gmail.com

Supervisor Signature: Date: 4/2/21

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HEAD OF DEPARTMENT / HEAD OF SCHOOL:** *(Where the HOD is Supervisor, the HOS must sign)***

Prof. Feroza Motara F. MOTARA 24/2/2021
(Name and Surname) (Signature) (Date)

DECISION OF CHAIR OF THE PG AFFAIRS:

Comments:

Signature: Date: