Consultation: Reviewing the safety and regulatory oversight of unapproved medicinal cannabis products

Submission to TGA

DRUG FREE AUSTRALIA

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EXECUTIVE SUMMARY

This document addresses three of the TGA consultation questions:

1. Contraindications for medical cannabis - see **Appendix A**
2. Claims for medical cannabis not supported by rigorous science - See **Appendix B**
3. Lack of quality assurance in the production of medicinal cannabis - See **Appendix C**

Appendix A gives extensive scientific evidence that cannabis is no longer fit for medicinal use, given advances in the science on cannabis via the vast population studies published in peer-reviewed medical journals between 2019 and 2025.

These population studies have at last verified what had been known since the 1970s from *in vitro* and *in vivo* research - cannabis is genotoxic, mutagenic, carcinogenic and teratogenic. This is through mechanisms first officially identified and given worldwide prominence in 2016.

Causal in double the number of cancers as tobacco, with a heavier disease burden in US States than the more extensively used tobacco, causal in pediatric cancers which make up 60-70% of pediatric cancer cases and attributable to parental cannabis use, causal in 89 of 95 birth defects tracked by European systems and registries, strongly causal in the current autism epidemic, causal in serious mental illnesses including psychoses, depression and suicide, and epigenetically passed to offspring for three to four generations, **Drug Free Australia contends that cannabis is no longer fit for medicinal use, given the very negative adverse event and side-effect profile.**

Appendix B provides an extensive summary of the 2017 US National Institutes of Health review of the science on medical cannabis which notably found a lack of properly conducted and rigorous scientific trials for medicinal cannabis. Once poorly designed and conducted trials were eliminated, there were very few conditions for which cannabis showed efficacy. ALso in **Appendix A** we demonstrate that cannabis is no better than placebo for chronic pain - the condition for which the majority of Australians are using medical cannabis.

Appendix C gives evidence from our US/Canadian affiliates of the lack of quality control in medicinal cannabis grow sites, with unacceptable contamination and use of dangerous pesticides. In this document we only present some examples of US incidents, while offering the TGA a much larger tranche of documentation on issues identified in such grow sites. Given that US and Canadian medical cannabis is accessed by Australians, the TGA does well to become familiar with these issues.

Our **recommendations** are found on page 8.

Introduction

Marijuana is one of the most commonly used drugs in the world. It is estimated that approximately:

- 9-10% of people using cannabis will develop an addiction (1 in 10 adults)
- 17% of adolescent users will develop an addiction (1 in 6 teens)
- 25-30% of daily or near-daily users will develop a cannabis use disorder

This risk of addiction however is not the only negative impact from using marijuana.
Studies have shown that the use of marijuana in children under the age of 18 can cause permanent problems with learning, as well as an increased risk of mental health issues, including schizophrenia. It also significantly increases the chances of addiction to any drug in the future.

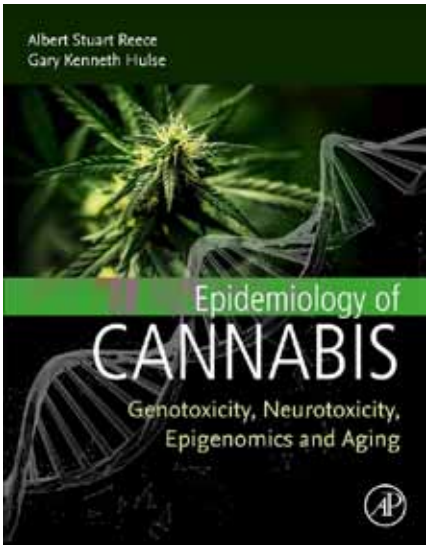
Since 2019 vast population studies of the entire US population and of populations across multiple countries in Europe have established such a wide range of conditions caused by cannabis that its role as a medicine must be re-evaluated by the TGA - where any other medicine with adverse events and a side-effect profile like that of cannabis would have historically been removed from the market.

In the 1980s, the average THC level in marijuana was relatively low, typically ranging from 1% to 2%. This is significantly lower than the levels found in many strains today, which can exceed 90%. The increase in THC levels is largely due to advances in cannabis cultivation and breeding techniques. Indoor growing techniques, selective breeding, and the development of new cannabis strains have all contributed to the higher THC levels seen today.

Clearly no assumptions can be made about cannabis based on decades-old data given the radical change in the substance itself.

This becomes even more relevant with the use of medicinal cannabis, where high doses of THC are now possible with preparations boasting purities of up to 99% THC. Given that medicines are often used more regularly throughout a day or week than recreational cannabis, any adverse events and negative side-effects will be magnified.

Elsevier publication released May 2025 - compiled population studies



This document will provide evidence that cannabis presents demonstrable damage to public health that far outweighs that of tobacco or alcohol.

What has now been demonstrated is that the genotoxic, mutagenic, carcinogenic and teratogenic nature of cannabis is not isolated to the users that consume it. Rather there is an epigenetic reach of these issues not only for the children of cannabis users, who already have significantly higher rates of pediatric cancers than children of non-users, but for grandchildren to the third and fourth generation.

Cannabis use was never victimless, but the sheer reach of problems arising from cannabis use for so many future innocent lives is a calculation the TGA, guiding Australian Territory, State and Federal governments, must now make.

Recent science - not fit for medical purposes

Our changed stance on medical cannabis

From 2003 to 2019 Drug Free Australia took a public position supportive of medicinal cannabis in line with the 2017 National Institutes of Health review - that cannabis should be supported for the very few conditions it does allevate but smoking is a wholly unacceptable mode of administration.

Our position changed when the first of the major US population studies, very strongly linking cannabis to autism, was published. And as with each of the subsequent population studies of entire populations in the US and Europe being published, our position has become more stridently opposed to the substance being used medicinally, with the only exception being children with epilepsy-like syndromes such as Dravet's syndrome of Lennox-Gastaut's. Even this position comes with some reservations.

Genotoxic nature known decades ago

For more than 50 years via *in vitro* and animal studies cannabis research has overwhelmingly demonstrated the genotoxic nature of cannabis.

The conclusion of an extensive 2009 review of 5,198 studies on cannabis concluded, "Chronic cannabis use is associated with psychiatric, respiratory, cardiovascular, and bone effects. It also has oncogenic, teratogenic, and mutagenic effects all of which depend upon dose and duration of use."

Population studies since 2019 confirm it

The recent massive population studies from all 50 States in the US (325 million people at close of study period) and from 14 European Union countries confirm what had been known for decades. ***A summary of the results are displayed centre-page.***

Strength of these studies

Since 2019 there are now 60 peer-reviewed population studies demonstrating that cannabis is causal in:

- **33 cancer types** as against 14 for tobacco (Cannabidiol [CBD] is the most carcinogenic cannabinoid [12 cancers])
- **cancers involved in 60-70% of all pediatric cases**
- **89 of 95 birth defects** tracked by European systems and registries
- **autism**'s exponential growth
- the growth in **serious mental illnesses** across the indices of depression and suicide
- **prematurely aging users** by age 30 by up to 30%
- **epigenetic heritability** of all the above from a cannabis patient to three or four generations of offspring, thereby multiplying harm

The 60 cannabis population studies are part of a larger suite of 160 studies by Australian researchers, Drs Stuart Reece and Gary Hulse from the University of WA/ Edith Cowan University.

All studies have been peer-reviewed and appeared in journals such as Nature - Scientific Reports, Science and the New England Journal of Medicine.

The same researchers gained significant worldwide media in 2016 when they were the first to publish the specific mechanism by which cannabis does such damage.

The cannabis studies, being geo-spatial over periods of years, allow a determination of causality once confounders are accounted for. Studies utilise causality-determining modalities devised by the TW Chan School

of Public Health and UCLA.

For fully cited evidence on every aspect see our 17 page document at Appendix A.

This evidence, which would greatly concern every Australian, is uniformly ignored by the Australian media, raising important questions of whether the media's large institutional shareholders may also be heavily invested in what has been the fastest growing industry in world history. Such a possible media conflict of interest makes the TGA even more important, because TGA determinations were never designed to be purchased by the highest bidder, but strictly according to the science.

Our larger document also deals with a wide variety of other issues relevant to this TGA Consultation and we encourage the TGA to consider the evidence therein.

Included in the document are:

1. the direct genotoxic mechanisms of cannabis

2. the latest review on caused psychosis studies

3. links between cannabis and violence

4. its involvement in violent homicide

5. discussion of unevidenced CBD claims

6. CBD as causal for autism

7. similarity of CBD symptoms to THC

8. CBD metabolising to THC

9. THC in hemp accumulating in the body

10. CBD being converted to Delta-8 THC

11. the failure of CBD to moderate chronic pain

12. the FDA's CBD bans due to lack of safety

13. animal products transfer CBD dangers

Quite apart from the unacceptable safety profile, all of the above create added concerns in relation to medicinal cannabis. We urge the TGA to look carefully into our evidence and to advise governments accordingly.

Lack of quality assurance in medical cannabis production

When GW Pharmaceuticals first did clinical trials with Epidiolex (now Epidyolex) it was able to announce a product of standardised purity, strength and dose achieved by strict quality assurance processes in the medication's production. The same is true of Satixex, despite its differences in THC and CBD levels.

This is what Australians expect of a medicine. But none of the other current cannabis products being imported from other countries worldwide under Special Access appear to adhere to such tightly monitored standards.

In **Appendix C** we deal with the extant problems with contaminants and dangerous pesticides being used in cannabis grow-sites.

The information in the first document in **Appendix C** is fairly comprehensive but Drug Free Australia has access to an extensive literature on specific problems as they relate to cannabis production in the US and Canada. We have appended two such examples of these more specific issues, with the offer to TGA of sending the entire body of literature on like incidents or examples of dangerous contamination and use of pesticides.

Drug Free Australia's considered stance is that the TGA should determine, after reviewing the science - particularly from the large population studies covered in the previous pages - that cannabis is no longer suitable as medicine, given an entirely unacceptable adverse event and side-effect profile. This determination should be made on its lack of demonstrated efficacy on most every condition for which it is prescribed, and where there are better alternatives available for those same conditions. Where cannabis may still be demonstrably effective, as for a smaller percentage of those suffering from child epilepsy-like conditions, Epidyolex has already met standards required by regulatory agencies worldwide and here for use in Australia.

Recommendations

1. **On the basis of comprehensive scientific evidence presented in this document at Appendix A, the adverse event and side-effect profile of medicinal cannabis is now so entirely unacceptable as to make it unfit for any medical use. This is before it is considered that there is only a demonstrated science supporting efficacy for a handful of medical conditions as identified by the US National Institutes of Health's extensive 2017 review which demonstrated the paucity of acceptably rigorous studies for medical cannabis versus many substandard studies to support its claims of efficacy - Appendix B. We note the lack of quality reviews of medical cannabis studies since 2017.**
2. **For those children with epilepsy-like conditions the TGA should continue to make Epidyolex available, given the data from its clinical trials and assured product quality.**
3. **All current cannabis medications coming from overseas should immediately become ineligible for Special Access, and only quality controlled Sativex and Epidyolex made available for end-of-life care for those conditions refractory to other treatments.**

Appendix A

The current science . . . how can cannabis possibly remain legal?

Massive population studies published in 2021 and 2022 for the US and Europe are confirming what in vitro and animal studies had shown decades ago - that cannabis causes many cancers, more than twice as many as tobacco, contributes to most birth defects, and accelerates aging by 30%.

Cannabidiol (CBD) is not exempt.

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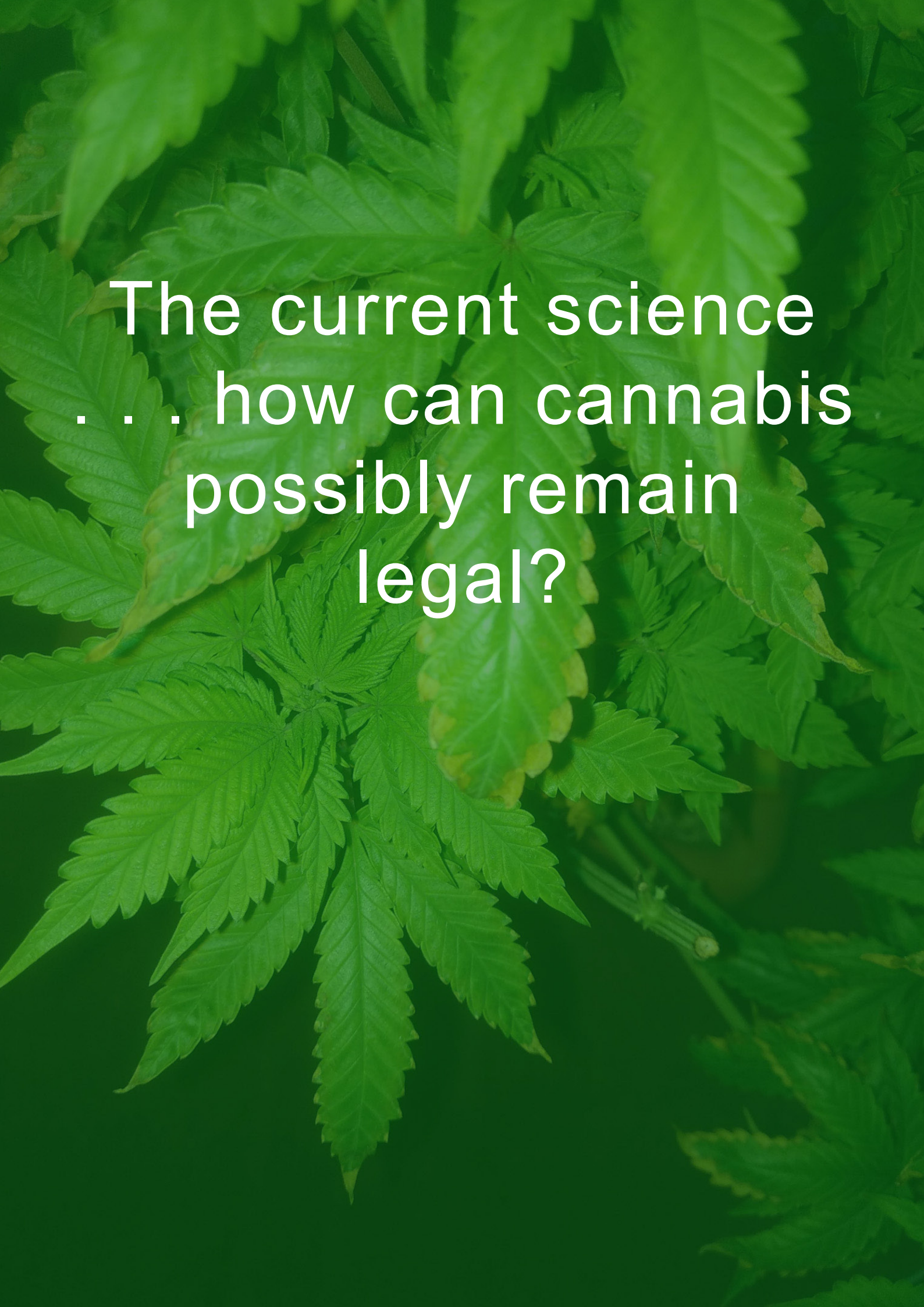
version 3.1

This document presents with URL links to the abundant science showing that cannabis delivers more death and damage than other illegal drugs such as heroin, speed, ice and cocaine, with the added deficit of deleteriously affecting any cannabis user's children and multiple generations to come.

It's medicinal benefits have been, perhaps purposely, over-hyped, and are far outweighed by its risks.

Legislators must act now.


The current science . . . how can cannabis possibly remain legal?

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Executive Summary

1. Research has established over a period of **50 years** that cannabis is genotoxic, mutagenic, oncogenic and teratongenic, meaning that **cannabis destroys genetic information in the cell, causing mutations which then cause cancers and birth defects.**
2. In 2021 and 2022, vast population studies for the entire US and also for 27 countries in Europe have demonstrated what in vitro and animal study research had already demonstrated, **that cancers, including childhood cancers, and birth defects had strongly elevated levels in those US States or European countries which have high cannabis use due to cannabis legalisation/liberalisation regimes**.
3. **Cannabis is causal in 33 cancers as compared to tobacco which causes 14.** Regulatory agencies would withdraw pharmaceutical drugs with this profile, and medicinal cannabis needs to be withdrawn, perhaps excepting children with epileptic-like seizures.
4. The **methodology** for these studies has been recorded in one of the world's top scienctific journals, **Nature - Scientific Reports.**
5. Recent population studies have demonstrated that **cannabis is contributing significantly to the autism epidemic.**
6. The studies demonstrate that birth defects are caused by the parental use of cannabis by both mother and father. This is due to **cannabis use literally shattering chromosomes,** where the body's DNA repair mechanisms sometimes fail, causing mutations. These mutations are passed on to future generations, with cannabis signifcantly degrading the human genome.
7. A recent phenomenon, which reprises the **Thalidomide** birth defects of 50 years ago, where babies are **born without limbs**, correlates strongly to areas where cannabis has been fed to farm animals and become part of the human food change. This again establishes the teratogenic nature of cannabis.
8. Research in 2022 also demonstrated that cannabis **prematurely ages** users by an accelerated 30%.
9. Older research has demonstrated that cannabis causes **30% of new psychosis/schizophrenia diagnoses in London, and 50% in Amsterdam.** It has also been shown to be causal in violence and homicide.
10. Despite public misunderstanding, medicinal cannabis carries all of the harms of recreational cannabis use - cancers, birth defects, aging, psychosis etc.
11. Cannabidiol **(CBD) is the most cancer-causing** of the cannabinoids in cannabis, c**ausing 12 of 27 cancers** identified in an early population study. It is also the major cannabinoid that is causal for autism and some other birth defects.
12. CBD can be converted in laboratories **into Delta-8-THC,** which is as psychactive and as dangerous as Delta-9-THC.
13. CBD can still contain small quantities of THC which due to the long half-life of the substance, can accumulate in the body. **CBD thereby does not exempt users from the dangers of THC.**
14. **Hemp seed food ingredients** also will have small quantities of THC which, because of the amounts consumed, **can deliver THC amounts in excess of limits set by specific US States.**

The latest science on cannabis and cannabinoids

Genotoxic nature of cannabis known for decades

For more than 50 years via *in vitro* and animal studies cannabis research has overwhelmingly demonstrated the genotoxic nature of cannabis.

The conclusion of an extensive 2009 review of 5,198 studies on cannabis concluded, "Chronic cannabis use is associated with psychiatric, respiratory, cardiovascular, and bone effects. It also has oncogenic, teratogenic, and mutagenic effects all of which depend upon dose and duration of use."

Thus there should be no surprises concerning what the latest vast population studies are demonstrating.

Population studies now confirm the research

2016 marked the year when the mechanisms behind the oncogenic, teratogenic and mutagenic nature of cannabis have been fully confirmed, and only since late 2021 and early 2022 that nationwide studies have been completed and published in medical journals which allow the full impact of cannabis use to be gauged at the population level.

Methodology published in top science journal

The various geospatial-temporal studies on the population impacts of cannabis have now been published in more than a dozen medical and scientific journals, with one of these studies with a clear explication of methodology, published in one of the world's top science journals, Nature - Scientific Reports.

For the first time geospatial-temporal programming has allowed previously unmanageable amounts of population data - specific nationwide diseases, differing cannabis use statistics by state or country, specific cannabinoids found in drug control seizures by jurisdiction, confounding other drug use, socio-economic confounders - to be combined to reveal cannabis health impacts. This has been combined with a whole range of tools - mixed effects, panel, robust and spatiotemporal regression modeling, inverse probability weighting and expected values (E-values) to make causal inferences, where E-values higher than 9 are considered high.

For the first time geospatial-temporal programming has allowed previously unmanageable amounts of population data to be combined to reveal cannabis health impacts.

Immense populations studied

A strength of these population studies is the very large populations of the US and multiple European countries studied, as well as the very significant numbers of cancer or birth defect incidence in any given year. For instance, the US expects more than 1.8 million new cancer diagnoses in a given year (2020) while these population studies typically work with 15 years of cumulative cancer or birth defect data.

Future generations adversely affected

Significant within these studies is the commentary on the epigenomic effects of cannabis indicating that the genotoxic damage of cannabis is passed epigenetically to future generations, raising ethical and moral concerns about its use either medically or recreationally given that its damages do not only affect the individual user. With 1,754 megabases of the 3,000 megabases of the total human genome liable to damage, 59% of the human genome is affected.

Research further shows that it is a mistake to believe that only the mother using cannabis while pregnant is responsible for intergenerational birth defects or pediatric cancers, as alterations to the father's sperm are also implicated.

Cannabis not fit for human consumption

Thus, the very recent science, which confirms what has been known for decades, now gives a clear understanding of the negative physical implications of any cannabis use, quite apart from the psychological damages. **It renders cannabis no longer acceptable for any kind of human consumption**. Perhaps the only defensible use remaining is for children with epileptic-like seizures where the benefits for the 40% that respond might arguably outweigh the risks.

It is crucial that legislators, media and regulators recognise that if smoking tobacco was recommended to alleviate any long-term medical condition it would never be treated seriously given the relationship between smoking and cancers. With cannabis, whether smoked or ingested, the relationship with cancers, birth defects and premature aging all persist.

The latest science

We will here cite summary text of the current science deriving from the many geospatial-temporal studies:

More than twice as many cancers as for tobacco

"These cancers have been causally associated with cannabinoids in studies based in the United States and Europe:

United States (25/28 cancers):
All cancer, acute lymphoid leukemia, acute myeloid leukemia, bladder, brain, breast, chronic myeloid leukemia, chronic lymphoid leukemia, colorectal, Kaposi, kidney, liver, lung, melanoma, myeloma, Hodgkins and non-Hodgkins lymphoma, esophagus, oropharynx, ovary, pancreas, prostate, stomach, testis, and thyroid;

Europe (33/40 cancers):
Acute lymphoid leukemia, acute myeloid leukemia, bladder, breast, chronic myeloid leukemia, chronic lymphoid leukemia, colorectal, hepatocellular, Kaposi, kidney, liver, lung, myeloma, melanoma, Hodgkins and non- Hodgkins lymphoma, esophagus, oropharynx, ovarian dysgerminoma germ cell tumor, pancreas, prostate, stomach, testis, non-seminoma of testis, and thyroid. In addition to those identified in the United States: Anus, penis, corpus uteri, gall bladder, larynx, mesothelioma, testis seminoma, and vulva."

There are 14 cancers historically tied to the use of tobacco, which these studies likewise find and thus confirm. However, with a total of 33 cancers likely caused by cannabis, there is more than a doubling of cancer risk presented by cannabis use as opposed to tobacco.

Cannabidiol (CBD) most implicated in cancers

Of the specific cancers related to cannabis as identified in these recent causal-inference studies, it is notable that all of the cannabinoids tracked within the studies contribute to cancer incidence. However, Cannabidiol (CBD), which is largely promoted as benign, is likely causal in twice as many cancer types than the psychoactive THC. This presents major risks to medicinal cannabis users who are moving more and more towards CBD preparations particularly as an adjunct to opiates for chronic pain.

Cannabis likely causal in pediatric cancer increases

A study published in the medical journal BMC Cancer in February 2021 demonstrated that rising rates of childhood cancers, which have increased by 49% since 1975 throughout the United States, are closely related to increased cannabis use in US States that have decriminalised or legalised cannabis for medical and recreational use. A causal relationship of cannabis to these cancers is demonstrated, indicating that cannabis particularly should not be used by women during pregnancy.

Data from the US Centers for Disease Control and Prevention (CDC) indicates that cancers such as leukemias, neuroblastoma, soft tissue sarcoma, lymphoma, testicular cancer and cancers of the brain and nervous system in under-20 year olds have all increased. These comprise 60-70% of all pediatric cancers, with previous studies linking many of them to parental cannabis use.

Pediatric cancers are conceptually important as they represent transgenerational and likely multigenerational transmission of heritable genotoxicity and epigenotoxicity.

Likely causal in 89 0f 95 birth defects

Most birth defects have now been linked to cannabis use. Again we cite the summary text of the current science.

"These systems and congenital anomalies have been causally associated with cannabinoids:

Systems found to be particularly affected in both the United States and Europe: Central nervous system, cardiovascular, chromosomal, orofacial, limb, gastrointestinal, uro-nephrological, body wall, and general;

Congenital anomalies found to be particularly affected in the United States: 46 of 62 anomalies;

Congenital anomalies and systems found to be particularly affected in Europe: 90 of 95 anomalies and systems:

Forty shared anomalies: anotia/microtia, interrupted aortic arch, aortic valve stenosis, atrial septal defect, atrioventricular septal defect, bilateral renal agenesis, bladder extrophy, choanal atresia, chromosomal anomalies, cleft lip and cleft palate, cleft palate alone, club foot, coarctation of the aorta, congenital cataract, diaphragmatic hernia, double-outlet right ventricle, Down syndrome (trisomy 21), Edward syndrome (trisomy 18), encephalocele, deletion 22q11.2, congenital hip dislocation, Hirschsprung's disease (congenital megacolon), holoprosencephaly, hypoplastic left heart, hypospadias, large intestinal/ rectal/anorectal atresia/stenosis, limb reduction anomalies, microphthalmos/anophthalmos, esophageal atresia/stenosis (+ tracheoesophageal fistula), omphalocele, Patau syndrome (trisomy 13), congenital posterior urethral valve, pulmonary valve atresia, single ventricle, small intestinal stenosis or atresia, spina bifida (without anencephalus), tetralogy of Fallot, total anomalous

pulmonary venous return, Turner syndrome (female X0), and ventricular septal defect."

We also note the March 2023 study of a subset of European birth defects in 14 countries which found cannabis causal in 62 of the 64 studied.

Limbless babies from cannabis in food chain

The latest research is uncovering the congenital anomaly effects of cannabis as it relates to the substance entering the food chain as feed for animals, where the animal products - meat, milk, cheese, eggs - are then consumed by humans. Of most concern is that food-chain cannabis is acting as the new Thalidomide, causing limblessness in human babies. A study published in the International Journal of Environmental Research & Public Health in September 2022 records,

Particularly concerning in this regard is the well documented exponential dose response of cannabis genotoxicity [12 – 18]. It might be reasonably expected that a marked jump in community cannabinoid exposure could be expressed as a switch like mechanism in epidemiological patterns of disease as indeed appears to have occurred recently in north-eastern France where both calves and human babies are suddenly being born without limbs at greatly elevated rates 60-times those of background [19–21]. There are indications that in these areas large crops of cannabis are being cultivated and food chain contamination seems likely. Since epidemiological studies have confirmed that the exponentiation of cannabinoid genotoxicity seen in the laboratory is also reflected in patterns of congenital anomaly incidence [1,3 ,4, 8, 22– 25] a relatively abrupt rise in community cannabinoid exposure would be expected to be associated with a relatively sudden and abrupt step-wise rise in congenital anomaly rates. This issue seems to not be well understood in the public health community.

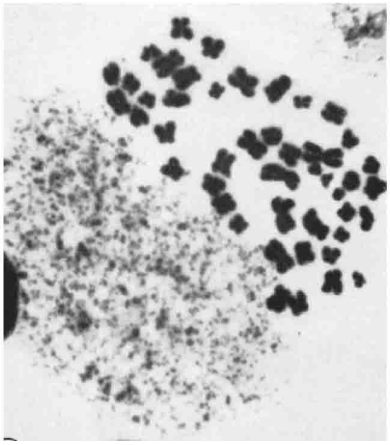


Fig. 1. Chromosomal Pulverization.
Original Report of Chromosomal Pulverization. Figure 7 , Kato H., Sandberg AA (1967). "Chromosome Pulverization in Human Binucleate Cells. Following Colcemid Treatment." J. Cell Biol. 34 (1): 35–45. Re-used by permission.

Cannabis use increases aging by 30%

"Fourteen lines of evidence for accelerated aging are linked to cannabis: cardiovascular age acceleration, cirrhosis and hepatoinflammation, chromosomal damage, a 30% advance in epigenetic clock age by late-generation DNA methylation clocks, changes to oocytes and sperm, endocrine disruption, genotoxicity and cancerogenesis, genotoxicity as congenital malformations, a 50% reduction in histones, mitochondrial inhibition, neuroinflammatory mental illnesses, elevated senescence and mortality, syndromic pattern of acute and chronic illnesses, and telomerase inhibition. These are not only age-defining illnesses but also age generating illnesses."

Major genotoxic mechanisms of cannabis

2016 marked the year that, like tobacco before it, the mechanisms by which cannabis causes cancer and birth defects were published.

Cannabinoids act directly on chromosomes, literally shattering or pulverising them. This process of 'chromothripsis', first discovered in 1967, should be able to be reversed by the body's DNA repair capabilities, which normally have sophisticated verification mechanisms with an error or mutation rate of 10^{-8}. In germ cells the rate is 100 times lower. Chromothripsis explains "the high rate of micronuclei, chromosomal fragments and abnormal chromosomes (truncated arms, chain and ring chromosomes and double minute circles) which are frequently seen in malignant tissues."

Chromothripsis, combined with epigenetic mechanisms which entail mutations being passed to future generations, well explains the mutagenic nature of cannabis, as well as the many congential abnormalities associated with its use.

Causes 50% of new psychosis in Amsterdam

At the Geneva Drug Convention deliberations in 1925 cannabis was first made illegal with the advice of Mr El Guindy from the Egyptian delegation being part of the evidence. El Guindy reported that cannabis could produce a delirium which "takes a violent form in persons of violent character" and also that "the addict very frequently becomes neurasthenic and, eventually, insane."

While the pro-cannabis lobby habitually ridiculed this evidence, saying it was as concocted as the 1930's movie *Reefer Madness,* scientific research has established that the original advice was correct.

The research link between cannabis and psychosis was first suggested in a 1987 Swedish study which found a 6 times elevated risk of schizophrenia for those who had used cannabis 50 times or more. Follow-up studies from the Netherlands by Van OS in 2002 and many since have now been verified in five major reviews.

The 2017 US National Academies of Science review of reviews found that,

The association between cannabis use and ***the development of a psychotic disorder*** *is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors. Factors contributing to the strength of the evidence derived from the cited systematic reviews include large sample sizes, the relative homogeneity of the findings, the presence of relationships between the dose/ exposure and the risk, the studies having been controlled for confounders, and*

the systematic reviews having assessed for publication bias. The primary literature reviewed by the committee confirms the conclusions of the systematic reviews, including the association between cannabis use and psychotic outcome and the dose-dependency of the effects, further bolstering the overall strength of evidence for our conclusions.

In a 2019 Lancet study by Kings College of London, Di Forti et al. determined that 30% of new psychoses/schizophrenia diagnoses in London, and 50% in Amsterdam were caused by high-THC forms of cannabis such as skunk.

The latest 2025 Annals of Internal Medicine review of 99 studies examining the effects of high-concentration THC products on mental health further reinforces the findings of prior systematic reviews that high concentrations of THC increase the risk for psychosis and schizophrenia.

Cannabis causal in bipolar development

The aforementioned 2017 review of reviews by the US National Academies of Science also concluded that,

*There is limited evidence of a statistical association between cannabis use and **the likelihood of developing bipolar disorder**, particularly among regular or daily users.*

Later studies, as detailed below, have given more weight to the 2017 review's finding.

On conversion to bipolar and schizophrenia

From the recent Elsevier book by Drs Reece and Hulse, *Epidemiology of Cannabis - Genotoxicity, Neurotoxicity, Epigenomics and Aging pp 58-9 there are some very notable observations,*

*. . . a Danish study reviewed all 6788 patients with drug-induced psychosis between 1994 and 2014. The overall conversion rate to a major psychotic disorder (bipolar disorder or schizophrenia) was 32.2% (29.7%– 34.9%). The highest conversion rate was for cannabis-induced psychosis (47.4%, 42.7%– 52.3%) converting to schizophrenia or bipolar affective disorder. Young age and self-harm were associated features that also elevated the risk of conversion to schizophrenia. **High-potency resin products increased this risk.***

They importantly note that,

Prolonged follow-up periods were required to detect these changes. The half time of conversion of schizophrenia was 3.1 years and to bipolar disorder was 4.4 years. The implication of this latter finding is extremely important as shorter follow-up studies would be less likely to detect these changes and report no adverse outcomes.

Serious problems for human development

From the same Elsevier publication above,

The impact of cannabis use on IQ (Intelligence Quotient) has been studied. In the aforementioned New Zealand study, long-term cannabis use from teenage years was associated with a 5.5 point decline in IQ testing. In another report, 70 individuals were studied in childhood and in young adulthood. While the IQ of the controls advanced 2.6 points across this period, that of the heavy cannabis users declined by 4.0 points so that at the end of the study the IQ of the controls was 11.3 points behind that of the nonexposed group.

From p 59 of the same publication,

In Ohio, USA, 204,780 youths with a diagnosis of mood disorder were followed up for (only) 1 year after their diagnosis. 60 Twenty-one thousand forty of these patients had a history of mood disorder. Within this cohort, the coexistence of cannabis use disorder was associated with a history of nonfatal self-harm (adjusted odds ratio 1.59, 1.13– 2.24), death by accidental drug overdose (2.40, 1.39– 4.16), homicide (3.23, 1.22– 8.59) and all-cause mortality (1.59, 1.13– 2.24).

Whether cannabis use be recreational or medicinal, these harms very much apply and should be of great concern for public health authorities and for any government seeking to protect population health.

Causal in serious mental illnesses

A number of the key Reece/Hulse population studies were in 2025 collated into the Elsevier book of 3,000 pages titled *Epidemiology of Cannabis - Genotoxicity, Neurotoxicity, Epigenomics and Aging*. In the opening chapter on Mental Illness and conclusions from their geospatial-temporal examination of US statistics at State and more granular Substate levels, there is a notable increase in serious mental illnesses as tracked in NSDUH data.

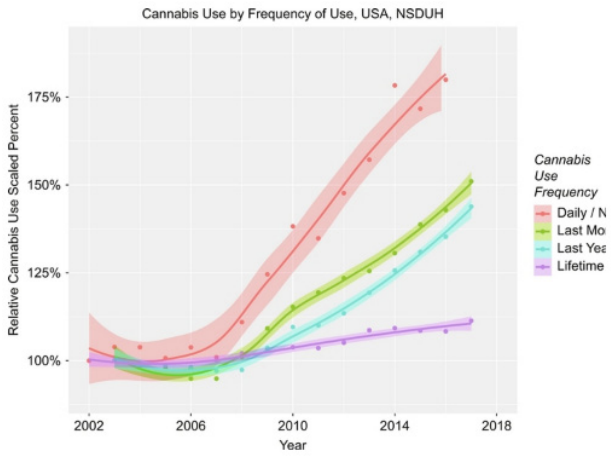
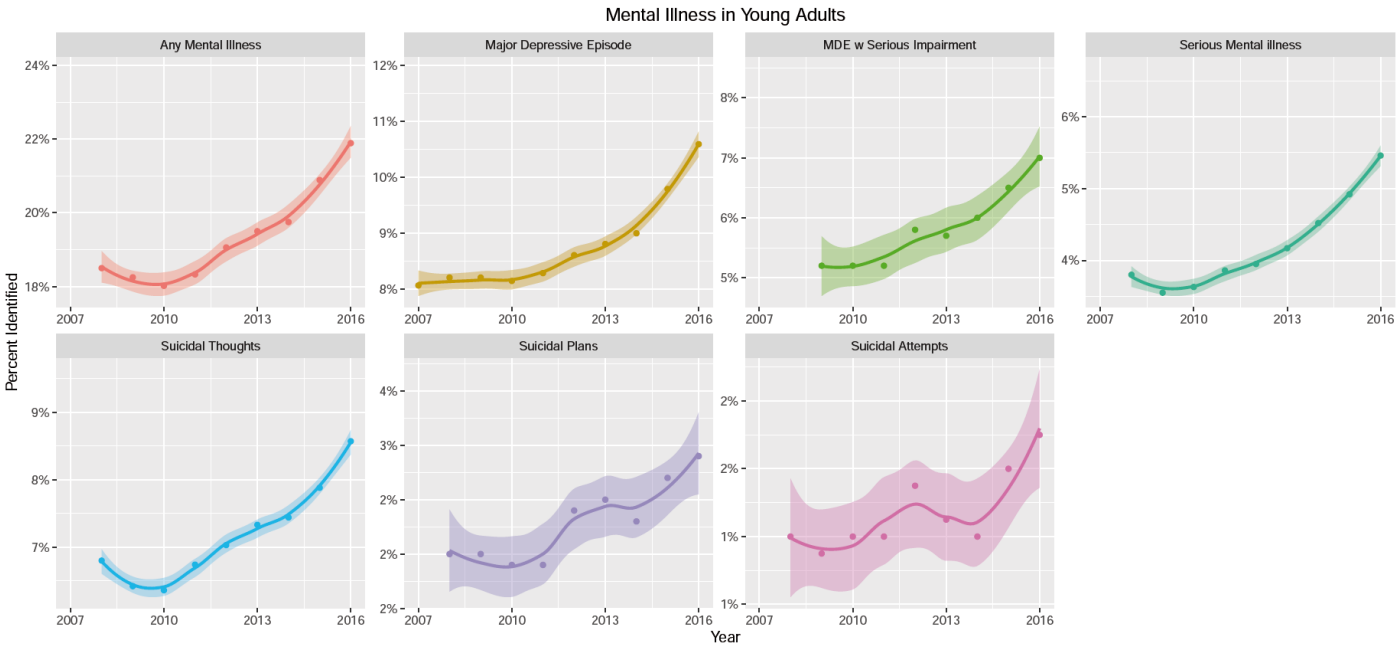


FIG. 6 Trends in cannabis use intensity over time.

On page 70, Reece and Hulse remark that:

SAMHSA datae showing that the US cannabis epidemic is primarily an epidemic of an increased intensity of cannabis use. Indeed on the basis of this data just this point was made recently by the United Nations Office of Drugs and Crime in their 2019 World Drug Report. Fig. 6 shows that while lifetime use has risen about 10%, daily or almost daily use has increased 80%.

The correlation with various mental illnesses between 2008 and 2017 can clearly be seen from the Figure 3 graphs in the same volume.



Using E-values to determine causality, developed by the TW Chan School of Public Health and UCLA, the study finds that,

Table 20 shows the E-values that apply to these results. One notes that all 14 of the minimum E-values are greater than the cut-off for causality which is 1.2599 and the minimum E-values range up to 6.71 × 106.

This indicates that there is a strong argument for the causality of cannabis regarding these indices of serious mental illness.

Cannabis causal in violence

The anecdotal evidence coming from women's refuges where staff report a strong representation of cannabis-induced violence from partners, albeit often from temporary cannabis withdrawal, has been demonstrated from research which has sought to exclude confounders such as alcohol use, antisocial personality syndromes and relationship satisfaction factors.

Other research into correlations between cannabis and violence has included longitudinal studies which look at the development of violent behaviours as they relate to cannabis use. Yet other studies examine the linkages between cannabis use and criminal behaviour.

Cannabis use and violent homicide

As a correlation that can only be examined after the fact, the evidence necessarily derives from court proceedings, most often tracked in newspaper articles. Extensive evidence for this correlation is found in the book by the former New York Times reporter Alex Berenson in his book "Tell you Children." One example amongst the dozens of reports and studies recorded in the book is that of Raina Thaiday, an Australian woman from Cairns, Queensland, responsible for murdering eight children, seven her own and one niece all at the one time. The court judgment stated that Thaiday,

"was suffering from a mental illness, paranoid schizophrenia, and that she had no capacity to know what she was doing was wrong."

and

"Thaiday gave a history of the use of cannabis since she was in grade 9 . . . . All the psychiatrists thought that it is likely that it is this long-term use of cannabis that caused the mental illness schizophrenia to emerge."

The linkage between psychosis/schizophrenia and homicide is as uncontroversial as that between cannabis and psychosis/schizophrenia. Thus court judgments that make the step of linking cannabis to homicide is founded on a weight of evidence.

The linkage between mass murders in the US and long-term cannabis use *is* controversial, but is currently being tracked for future study.

What we already knew about cannabis

Decades of research on cannabis have indicated a long list of harms.

- Cannabis is an established gateway to other dangerous drugs, adding an additional gateway beyond the two existing legal drugs
- Cannabis users are 50% more likely to develop alcohol use disorder
- Cannabis is associated with Amotivational Syndrome
- Cannabis use is associated with a 3 fold risk of suicidal ideation
- Brain Function
  - Verbal learning is adversely affected
  - Organisational skills are adversely affected
  - Cannabis causes loss of coordination
  - Associated memory loss can become permanent
  - Cannabis is associated with attention problems
- Drivers are 16 times more likely to hit obstacles
- Miscarriage is elevated with cannabis use
- Fertility is adversely affected
- Newborns are adversely affected with appearance,

weight, size, hormonal function, cognition and motor function adversely affected through to adulthood
- Cannabis use causes bronchitis
- Testicular cancer is associated with cannabis use
- Cannabis is also associated with cardio-vascular stroke and heart attack, with chance of myocardial infarction 5 times higher after one joint

According to the most authoritative 2017 review on cannabis by the US National Academies of Medicine, medicinal cannabis had scientific support for the treatment of only the following:

- Chronic pain – modest effect only
- Nausea – with most other available options more effective
- Multiple Sclerosis (MS) – modest effect only
- AIDS wasting – with many other better options available
- Tourette Syndrome
- Post Traumatic Stress Disorder (PTSD)
- Traumatic brain injury, intracranial haemorrhage

Treatment of childhood epilepsy-like syndromes via the use of CBD-based Epidiolex was demonstrated after 2017.

Medicinal cannabis carries all the harms

For all the harms of cannabis that have come to light through careful research, the persistent perception amongst the public is that any harms to recreational users do not in any way accrue to medicinal cannabis patients.

Nothing could be further from the truth. Excluding preparations high in CBD, most medicinal cannabis products have elevated THC, the psychoactive cannabinoid considered most likely to cause psychoses. At the same time, all the other cannabinoids which cause the conditions laid out in this document are present and active, again in more concentrated forms than in cannabis that was smoked in the 1960s.

Accidental ingestion by children

In a study of children hospitalised for cannabis exposure - between 2008 and 2019 there were 1,898,432 adolescent hospitalisations in 18 states and Washington, DC, with 37,562 (2%) of those hospitalisations having a cannabis-related diagnosis - 8,457 (23%) in states with no legal use, 20,444 (54%) in medical use only states, and 8,661 (23%) in states (NMCL) where recreational cannabis use had been legalised. The conclusion of the study was that,

Conclusions: Cannabis-related adolescent hospitalizations at children's hospitals are increasing, with a disproportionate increase postlegalization in states with NMCLs. Interventions are warranted to increase cannabis use identification and treatment among at-risk adolescents in the hospital-based setting.

The reason for the many hospitalisations is that THC edibles "can be easily mistaken for commonly consumed foods such as breakfast cereal, candy, and cookies, and accidentally ingested," says the US FDA. (quoted from FDA Powerpoint presentation 27/10/2022 - "Understanding FDA's Approach to Cannabis Science, Policy, and Regulation). The FDA further blames cannabis products with logos that appear similar to regular foods, causing children to ingest often in error.

Adverse events include hallucinations, elevated heart rate and vomiting.

Medicinal cannabis often poorly regulated

A problem reported from the US which appears to be a likely issue in other countries like Australia with reduced regulatory commitment is that independently tested medicinal cannabis products are frequently tainted with mould and other toxins such as pesticides.

A report from California cites 80% of medicinal cannabis products being tainted when tested by Anresco Laboratories at a Hempcon event in the Bay area.

Because cannabis appears to be given a pass that no other medicinal product is ever given - without being tested for strength, purity and dose or testing via clinical trials - there are unknowns as to the long-term health deficits of these unregulated products.

It also raises serious questions as to why cannabis is getting such an easy pass from regulatory agencies which only a few years back were rigid in any requirements concerning any drug or food additive.

Regulatory agencies not doing their job

The latest science clearly shows that cannabis is not fit for human consumption. It is mutagenic, oncogenic and teratogenic, with mechanisms that also prematurely age users. It is also clear that the physiological impacts of cannabis are not rare side-effects, but harming very significant numbers of users as well as future generations.

Any regulatory agency that is faced with this level of inflicted harm, particularly as it relates to a medicinal product, would either issue black box warnings or would withdraw the product from the market.

The fact is that there is significant investment, and influential investors in cannabis would never in the past have been allowed any easy pass. Today our regulatory agencies appear to be captured by monied interests, unwilling to do anything because there is a simple lack of public scrutiny.

Media not doing its job

The lack of media attention to the science which is continually advancing on cannabis, with results that would alarm the public if properly reported, is leading to a situation where many lives are being put at risk for the sake of monied interests. The media has traditionally had a role of reporting the news dispassionately, but more often makes reports on the harms of cannabis and cannabinoids as insignificant as possible.

Alternate pathways needed for publicity

If the media is not going to do its job, drug prevention organisations are forced to use alternate media pathways to disseminate the science on cannabis harm.

The latest science on Cannabidiol (CBD)

The largely unevidenced promotion of CBD

Cannabidiol (CBD) has been aggressively promoted to the public as a substance with miraculous properties. Even those articles that claim scientific support use mostly very limited studies which lack the rigour of random control trials. For instance, Forbes magazine listed the scientifically-verified conditions alleviated by CBD use as anxiety and depression, childhood epilepsy-like conditions, PTSD, opioid addiction, ALS, unmanageable pain, diabetic complications, protection against neurological diseases and arthritis. This list is conservatively short as compared to its advertised benefits on internet advertising services, where every malady seemingly finds its answer in this wonder drug - even as a cure to cancer.

The common experience with claims about cannabis has been that when rigorous clinical trials are conducted, the claims evaporate. This is best evidenced by the 2017 National Academies of Medicine review of cannabis, led by a committee of 16 professors and epidemiologists and 15 reviewers of similar qualification. Very few claims for cannabis were found to have rigorous research support. And on the contrary, when it comes to scientific rigour, CBD is generally the most lethal of the cannabinoids.

Genotoxicity of CBD uncontroversial

Dr Stuart Reece, a Professor at the University of Western Australia and possibly the world's most authoritative source on cannabis physiology and biochemistry, has confirmed that the genotoxicity of CBD is uncontroversial. Dr Reece, along with Dr Gary Hulse, is well-published in areas such as cannabis genotoxicity, teratology and epigenetics.

In e-mail communication with Drug Free Australia dated 27June 2019 Dr Reece confirmed that the CBD effect on mitochondria is highly significant, well recognised and uncontroversial. He further stated that it is now accepted that mitochondrial toxicity can become reflected in genotoxicity also through the balance mechanisms between mitochondria and nucleus, which is likewise uncontroversial.

Notably, the genotoxicity of CBD is admitted in authorised prescribing information with the US FDA and with the European Medicines Agency. It even appears on the labels of hemp oil marketed by Woolworths in Australia.

CBD the most carcinogenic cannabinoid

In the first run of data on US cancer rates as they relate to cannabis use across the various state drug policy regimes, CBD was found to be the most carcinogenic of the cannabinoids selected for inclusion in the study, with CBD likely causal in 12 of the 27 cancers there confirmed as compared to 7 for THC.

. . . CBD was found to be the most carcinogenic of the cannabinoids selected for inclusion in the study, with CBD likely causal in 12 of the 27 cancers as compared to 7 for THC.

As is the case with tobacco, which was likewise verified in the study to be causal in 14 cancer types, any health authority would not allow it to be marketed as the cure for numerous maladies given the risks it presents.

Precisely the same should be the case with CBD products, where Australia's regulatory body was informed in 2021 of the carcinogenic nature of CBD, but nevertheless moved shortly thereafter to remove regulatory strictures on its availability, leading to serious questions about the TGA's current philosophy on safety.

CBD implicated in autism epidemic

The often-voiced claim that CBD is benign, presenting no significant harms to a patient, needs to be reassessed in the light of an evolving science on CBD.

In a recent letter to the New England Medical Journal, Dr Stuart Reece and his research colleague Dr Gary Hulse wrote the following,

As one of the major cannabinoids and a high-dose ligand at CB1R's cannabidiol is implicated in the close spatial (northeast USA), temporal (recent years) and demographic (young adults) association between cannabis use and mental illness chronicled by SAMHSA and the nationwide surge in autism recently linked to cannabidiol.

CBD is more strongly implicated in autism prevalence than THC, and cannabis moreso than opiates according to this study. This has been established by waste-water data which establishes the strength of THC and various other cannabinoids in cities across the US correlated against increases in autism in those US States that have legalised access to recreational and medicinal cannabis.

CBD more causal in certain birth defects

Reece and Hulse, in their aforementioned letter to the New England Journal of Medicine assert the following:

Cannabidiol is a known chromosomal clastogen, epigenotoxin and mitochondrial toxin and was linked to the 29% surge in Colorado birth defects, led by cardiovascular defects, just as in Canada; and the pattern of rise of Downs syndrome, anotia and absent arms in Alaska and Oregon; and parts of France after it was added to the food supply; or the emergence of new cannabis-related defects like atrial septal defect in Colorado, Alaska, Oregon, Kentucky and Hawaii.

While cannabis is implicated in growing rates of gastroschisis (a birth defect where babies are born with their intestines outside the body) in States and countries which are legalising cannabis for medical and recreational use, it is CBD moreso than THC that appears causal in these population studies.

In e-mail communication dated 21 January 2019 between Drug Free Australia and Dr Stuart Reece who was one of the researchers that uncovered the association between cannabis and gastroschisis, Reece stated that,

The order of potency for both gastroschisis and autism is CBD>THC>Opioids.

This statistical finding alone suggests more study needs to be done on CBD's relationship to birth defects, given the known DNA damage it has been demonstrated to cause.

CBD symptoms similar to THC

Research published in the journal Cannabis and Cannabinoid Research shows that more than 40% of children with epilepsy who were given CBD orally had adverse events that included THC like symptoms. The research challenged the widely accepted premise that CBD is not intoxicating. There is evidence that CBD is biotransformed to metabolites that have similar effects as THC.

Notably, the FDA-listed Adverse Reactions for CBD include THC-like symptoms such as suicidal ideation, depression and anxiety. Their advice is as follows:

Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27863 AED-treated patients was 0.43%, compared to 0.24% among 16029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

More studies needed - CBD/THC metabolism

Concerning the transformation of orally-ingested CBD into THC, even the US Hemp Connoisseur magazine recognizes that more study is needed. They write:

Much research has involved the administration of THC and CBD to patients for symptoms such as fibromyalgia, Crohn's disease and insomnia, but researchers have been circumspect in declaring their results and have called for further testing. Watanabe's research, though conducted on mice, may hold true for humans – but that must be the subject of future studies. As Georgetown University Medical School's Dr. Robert du Pont pointed out, there are an estimated 400 components in the cannabis plant, making it difficult to determine exactly which component is providing relief when cannabis is ingested for medical reasons.3

Could anomalies in results have resulted from the way gastric juices break down CBD within the human body? In a 2016 study published in Cannabis and Cannabinoid Research, by John Merrick and associates, it was noted that, "In recent epilepsy research, pediatric subjects receiving orally administered CBD showed a relatively high incidence of adverse events (≤44%), with somnolence (≤21%) and fatigue (≤17%) among the most common."4 This led the researchers to more closely investigate the accepted premise that CBD is non-psychoactive. They came to the conclusion that, "Gastric fluid without enzymes converts CBD into the psychoactive components Δ9-THC and Δ8-THC, which suggests that the oral

route of administration may increase the potential for psychomimetic adverse effects from CBD.

THC in CBD hemp accumulates in the body

It is important to recognise that CBD, a product of low THC hemp where THC cannot exceed 0.3%, nevertheless will most likely have these low quantities of THC present. A Health Canada study recognises the issues around THC accumulation in the body thus,

According to Canada's national health department, Health Canada, "In theory the ripened seeds of Cannabis contain no detectable quantity of THC. However, because of the nature of the material it is almost impossible to obtain the seeds free from extraneous THC in the form of residues arising from other parts of the plant which are in close proximity to the seeds. Although it is required for the seeds to be cleaned before any subsequent use, the resinous nature of some of the material makes complete cleaning extremely difficult."

Since THC and the over 60 other cannabinoids are fat-soluble, i.e., store themselves in the fatty tissues of the brain and body, even a very small amount may be damaging, especially if ingested regularly. Fat-soluble substances accumulate in the body.

THC has a half-life of about seven days, meaning that one-half of the THC ingested or inhaled stays in the brain and body tissue for seven days. Traces can stay in body tissues for a month or more. The only important substance that exceeds THC in fat solubility is DDT.

A risk assessment done for Health Canada states that, "New food products and cosmetics made from hemp – the marijuana plant – pose an unacceptable risk to the health of consumers. It also says that hemp products may not be safe because even small amounts of THC may cause developmental problems. "Those most at risk," the study says, "are children exposed in the womb or through breast milk, or teen-agers whose reproductive systems are developing."

"Hazards associated with exposure to THC include acute neurological effects and long-term effects on brain development, the reproductive system and the immune system," the study says. "Overall, the data considered for this assessment support the conclusions that inadequate margins of safety exist between potential exposure and adverse effect levels for cannabinoids (the bio-active ingredients) in cosmetics, food and nutraceutical products made from hemp."

Hemp THC ingestion beyond health limits

Quite apart from accumulations of THC in body fats and the health risks presented by it, there is another issue of large quantities of hemp ingredients being used in hemp edibles. The following demonstrates that a serving of hemp seed flour chips can have, despite being 0.3% THC, 8 times as much THC allowable for a typical serving. Add to this the accumulation of cannabinoids as described at our previous heading, and there is real cause for concern about hemp edibles opening up the consumer to various dangers caused by THC.

Using what I call "Farm Bill Math", the definition for hemp in the 2018 Farm Bill allows for 3 milligrams (mg) of THC per gram (same as 1,000 milligrams) by product weight. At face value, this may not seem like a big deal, until one realizes the weight of many food products that we and our children consume. For example, a bag of Tostitos Corn Chips specifies that one serving size is 7 chips, which has a listed weigh of 28 grams. Thus, each chip would weigh about 4 grams (28 grams divided by 7 chips). Assuming that these chips could be made from hemp seed flour, one chip could legally contain up to 12 mg of THC (4 grams X 3 mg/gram). Also consider the 28 grams serving size, or 7 chips, noted on the Tostitos bag. This serving size could contain up to 84 mg of THC (28 grams X 3 mg THC/gram)! Corn chips also contain very little moisture in the form of water (low dry weight); it is only about 1% to 2.5%, so likely hemp-based chips would be very similar.

It is important to keep in mind that in Colorado, a product that contains THC is limited to 10 mg per serving for public health and safety reasons. Therefore, in Colorado, only one hemp-based corn chip (containing 0.3% THC by dry weight) would be roughly equivalent to the legal serving size of THC.

CBD can be readily converted to Delta-8-THC

From the University of Connecticut, commenting on Δ8-THC, which is equally as psychoactive as Δ9-THC, being produced from hemp, and the differing legalities across US states. This is just another way that unregulated CBD can produce an illicit recreational product.

Newswise — One is an illegal drug found in marijuana while the other is marketed as a safe herbal alternative. But the claimed differences between them aren't backed by science, a group of UConn researchers report on Nov. 1 in Drug and Alcohol Dependence.

Tetrahydrocannabinol, or THC, is the psychoactive compound produced by cannabis plants. The federal government lists Δ9 -THC (pronounced delta-9-THC) on the Schedule 1 list of dangerous drugs with no accepted medical use. But other versions of THC that differ only by the location of a double bond, such as Δ8-THC, remain quietly quasi-legal on the federal level.

The legality differences between the various versions of THC are causing conflict between the hemp and cannabis industries. There is also potential for harm to consumers. Although Δ8-THC is viewed as an herbal extract of hemp, many manufacturers use solvents and chemical processes that can leave harmful residues in the product, and there are no standards for purity or safety. Because there are no limits, some products contain ridiculously high levels of Δ8 and other THC variants that could potentially cause harm due to the sheer dosage. And states do not agree on its safety or legality. Some states, such as Connecticut, have made Δ8-THC as controlled as Δ9-THC, while in others it remains legal. Cannabis producers allege the distinction is giving rise to unfair competition between the hemp and marijuana markets.

If regulating Δ9-THC as an illegal drug is based on the fact that it has physical and psychoactive effects, then the first step to rational regulation of Δ8-THC would look at whether it, too, has those effects. And people who have experience with both say it does; most agree the effects of Δ8 are similar to Δ9.

CBD no better than placebo for pain

Given that CBD is increasingly being marketed as a safe and effective substance for pain relief, there is an increasing amount of research coming to hand demonstrating that CBD is ineffective. A JAMA review of 20 studies found that CBD is no more effective than placebo.

The conclusion of this review was surprising but quite self-evidently correct, emphasising the inordinate levels of expectation for cannabis due to the unevidenced hype continually generated by the cannabis industry and an unquestioning and therefore complicit media,

The findings of this systematic review and meta-analysis suggest that placebo responses contribute significantly to pain reduction in cannabinoid clinical trials. The unusually high media attention surrounding cannabinoid trials, with positive reports irrespective of scientific results, may uphold high expectations and shape placebo responses in future trials. This influence may impact the outcome of clinical trials, regulatory decisions, clinical practice, and ultimately patient access to cannabinoids for pain relief.

Other related studies are determining no benefit for CBD with final stage cancer patients as it relates to the alleviation of pain, depression, anxiety and quality of life.

When it is considered that more than 50% of Australians use cannabis for chronic and another few percent for cancer pain relief, the role being given to a substance such as CBD with its many physiological dangers is inordinately great, and frankly alarming.

US FDA CBD bans due to lack of safety

The US Food and Drug Administration (FDA) has been continuing to monitor the safety of CBD and lists the current concerns below. It must be noted that there is still extensive research to be done to establish the real harms or otherwise of many of their concerns, which, it must be noted, have not reckoned with the most recent science on CBD as reported in this document. Adverse event reports follow.

We posted scientific questions about CBD safety related to:

- The risk of liver injury
- Toxicities of active metabolites, e.g. 7-COOH-CBD
- Impact on the male reproductive system
- Effect of co-administration with other substances
- Impact on neurological development
- Sedative effects, including effects on driving and operating heavy machinery
- Transdermal penetration and pharmacokinetics
- Long-term (chronic) repeated dose toxicity studies
- Effect of different routes of administration (e.g., oral, topical, inhaled)
- Effect on pets and food-producing animals
- The potential for bioaccumulation of CBD
- Effect on the eye

Figure 1. Number of exposure calls involving cannabidiol to U.S. Poison Control Centers by year: National Poison Data System 2014-2019

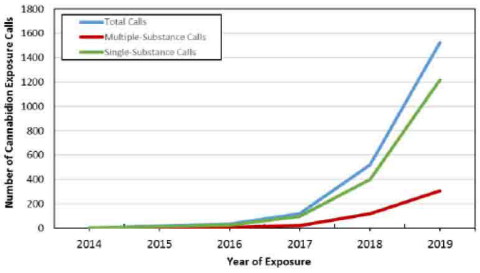
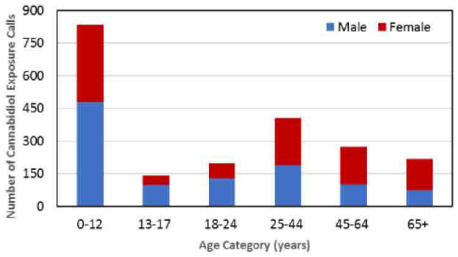


Figure 2. Exposure calls involving cannabidiol to U.S. Poison Control Centers by sex and age category: National Poison Data System 2014-2019



Dara on sex and/or age unknown for n=149 cannabidiol exposure calls

Figure 3. Formulation in exposure calls involving cannabidiol to U.S. Poison Control Centers: National Poison Data System 2014-2019

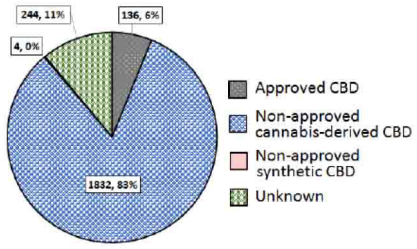
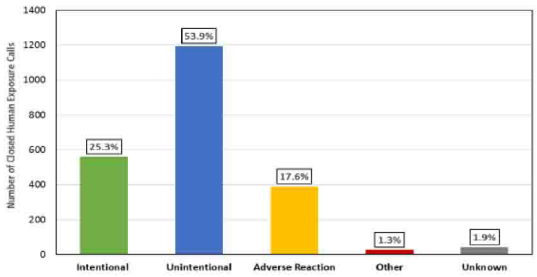


Figure 4. Reasons for exposure among U.S. Poison Control Center calls involving cannabidiol: National Poison Data System 2014-2019



Animal products transfer CBD dangers

As previously recorded in this document, cannabinoids entering the food chain with hemp being introduced as animal feed, presents genuine risks to humans. This may not only be through the Thalidomide-like phenomenon of human babies being born without limbs, but may have other manifestations given the accumulation of cannabinoids in the body. The US FDA has ruled that hemp feed and CBD 'medication' cannot be used with animals that are part of the human food chain.

The U.S. Food and Drug Administration (FDA) has issued warning letters to four companies illegally selling unapproved animal drugs containing cannabidiol (CBD) that are intended for use in food-producing animals. The companies include Haniel Concepts dba Free State

Oils, Hope Botanicals, Plantacea LLC dba Kahm CBD and Kingdom Harvest. While the FDA does not know the current extent of CBD use in food-producing animals, the agency is taking steps regarding these unapproved and potentially unsafe products now to help protect animals and the safety of the food supply.

Unapproved drugs like these CBD products have not been evaluated by the FDA to determine whether they are effective for their intended use, what the proper dosage might be, how the products could interact with FDA-approved drugs, or whether they have dangerous side effects or other safety concerns.

The FDA is concerned about these CBD products for food-producing animals not only because CBD could pose a safety risk for the animals themselves, but also because of lack of data about the safety of the human food products (meat, milk and eggs) from the animals that have consumed these CBD products.

Regulatory agencies not doing their job

The latest science clearly shows that hemp and CBD is not fit for human consumption. It is mutagenic, oncogenic and teratogenic, and is a contributor to the premature aging processes likely caused by cannabis. It is also clear that the physiological impacts of cannabis are not rare side-effects, but harming very significant numbers of users as well as future generations.

Any regulatory agency that is faced with this level of inflicted harm, particularly as it relates to a medicinal product, would either issue black box warnings or would withdraw the product from the market.

The fact that there is significant investment, and influential investors in cannabis would never in the past have allowed cannabis a pass. Today our regulatory agencies appear to be captured by monied interests, unwilling to do anything because of a lack of public scrutiny.

Media not doing its job

The lack of media attention to the science which is continually advancing on hemp and CBD, with results that would alarm the public if properly reported, is leading to a situation where many lives are being put at risk for the sake of rich investors. The media has a role of reporting the news dispassionately, but more often makes reports on the harms of cannabis and cannabinoids as insignificant as possible.

Alternate pathways needed for publicity

If the media is not going to do its job, drug prevention organisations are forced to use alternate media pathways to disseminate the science on cannabis harm.

To this end an Australian Taskforce of drug prevention agencies is seeking crowdfunding to ensure that the public can be exposed to the current science.

Appendix

A more potent carcinogen than alcohol or tobacco

The following pages provide the full analysis from the most recently published (July 2023) European cancer data demonstrating that cannabis is a ***more potent carcinogen than either alcohol or tobacco***.

It is notable that the methodology of the Reece/Hulse geo-temporal-spatial studies is confirmed by their results for alcohol and tobacco, which conform with the already established science on these other substances.

Following pages display the text and tables confirming the carcinogenic relative potency of cannabis.

As New Zealand outlaws lifetime consumption of tobacco for young people on the grounds that it causes too high a mortality, Australian governments needs to face the overwhelming evidence that cannabis, including hemp CBD, is likewise causal in unacceptable mortality.

Table 9. Summary table for positive significant terms in additive panel model.

Term	Count	Negative Total of *p*-Value Exponents	Mean of the Negative *p*-Value Exponents	Median of the Negative *p*-Value Exponents	Total of the Lower E-Value Exponents	Mean of the Lower E-Value Exponents	Median of the Lower E-Value Exponents
Last Month's Cannabis	19	189	9.95	8	341	17.95	17
Herb. THC	21	551	26.24	18	165	7.86	7
Resin. THC	5	13	2.6	2	5	1.00	0
Income	7	29	4.14	5	1	0.14	0
Alcohol	4	17	4.25	2	0	0	0
Tobacco	14	55	3.93	2.5	0	0	0

Table key: Term—Relates to the number of models which include the cited independent covariate as significant. The other columns in this table relate to the described parameters (see text).

3.3.2. Interactive Panel Modelling

No Temporal Lags (Unlagged)

A three-way interaction term was introduced between tobacco use, last month's cannabis use and the THC concentration of cannabis herb into the above additive model. The output from this model is shown as Supplementary Table S27. Significant terms are extracted (Table 10) and summarised in tabular (Table 11) and graphical (Figure 14) formats. Table 10 is ordered by descending minimum E-value. It is clear from this table that cannabis terms dominate the top of this table and tobacco terms are near the bottom. These findings are reflected in the tabular and graphical summaries provided (Table 11 and Figure 14), which again show that the effect of terms, including cannabis, are much more potent than the known carcinogens tobacco and alcohol.

Two-Year Temporal Lags

This modelling procedure was repeated at two years of temporal lags. Model output appears as Supplementary Table S28 and the reduced tabulation consisting of significant positive terms appears as Supplementary Table S29. The terms of Supplementary Table S29 are then summarised in Supplementary Table S30 and displayed graphically in Supplementary Figure S24. It is again noted that the cannabis terms preponderate over tobacco, alcohol and income terms in all four panels.

Four-Year Temporal Lags

The above-described interactive panel model was run at four years of temporal lag. Full model outputs are shown in Supplementary Table S31, the reduced model with positive significant terms is shown in Supplementary Table S32 and the summary of this model appears in Supplementary Table S33 and Supplementary Figure S25. From Supplementary Figure S25, it is clear that the sum of the negative *p*-value exponents is greater for tobacco than for the other covariates. However, for the other three metrics, it is clear that the impact of the measures of cannabis predominate.

Six-Year Temporal Lags

A similar exercise was conducted at six years of temporal lags. Interactive panel model output appears as Supplementary Table S34, positive and significant terms are shown in Supplementary Table S35 and these are summarised by term in Supplementary Table S36 and Supplementary Figure S26. Cannabis-related terms again predominate in all four panels. For both the numbers of cancers implicated and the total of the negative *p*-value exponents, tobacco comes in second place for terms related to cannabis exposure.

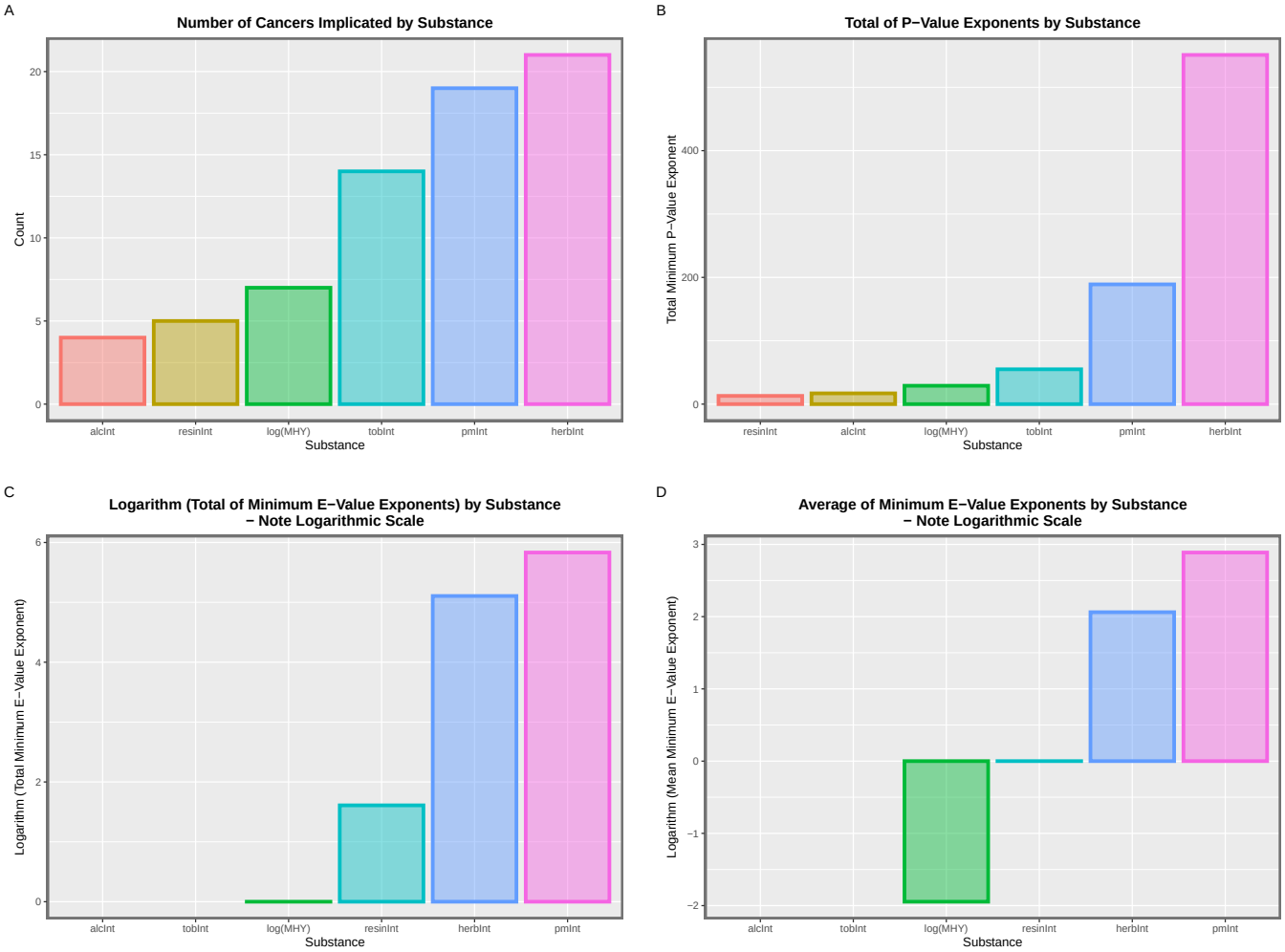


Figure 13. Graphical summary of additive panel model. (**A**) number of cancers implicated by substance, (**B**) Totals of (negative) *p*-value exponents by substance, (**C**) Logarithm (total of minimum E-Value Exponents) by substance—note logarithmic scale and (**D**) average of minimum E-value exponents by substance—note logarithmic scale.

Table 10. Significant positive terms from interactive panel regression.

Cancer	Term	β-Estimate	Std. Error	*p*-Value	Adj. P. FDR	Adj. P. Holm	E-Value Estimate	E-Value 95% Lower Bound
Colorectum	Herb. THC	55.387	5.081	1.17×10^{-26}	1.13×10^{-25}	3.14×10^{-24}	8.51×10^{30}	2.72×10^{25}
Breast	Herb. THC	37.005	3.771	4.69×10^{-22}	3.59×10^{-21}	1.22×10^{-19}	7.65×10^{27}	2.43×10^{22}
Gallbladder and Biliary	Herb. THC	20.744	2.892	1.41×10^{-12}	6.28×10^{-12}	3.28×10^{-10}	1.84×10^{26}	1.53×10^{19}
Oropharynx_Broad	Herb. THC	23.856	4.274	4.15×10^{8}	1.24×10^{-7}	8.26×10^{-6}	1.31×10^{26}	1.17×10^{17}
All Cancers	Herb. THC	12.034	2.019	4.45×10^{9}	1.46×10^{-8}	9.26×10^{-7}	1.41×10^{23}	4.48×10^{15}
Thyroid	Herb. THC	20.386	3.101	7.61×10^{-11}	2.80×10^{-10}	1.67×10^{-8}	2.72×10^{21}	1.40×10^{15}
Anus	Herb. THC	13.789	2.229	8.74×10^{-10}	3.03×10^{-9}	1.86×10^{-7}	1.74×10^{20}	8.63×10^{13}
Testis	Herb. THC	33.843	6.241	7.22×10^{8}	2.03×10^{-7}	1.39×10^{-5}	5.43×10^{17}	2.80×10^{11}
Stomach	Herb. THC	24.735	4.252	7.31×10^{9}	2.28×10^{-8}	1.49×10^{-6}	4.63×10^{16}	1.46×10^{11}
Oropharynx	Resin. THC	7.349	0.625	4.34×10^{-22}	3.40×10^{-21}	1.13×10^{-19}	1.92×10^{11}	2.86×10^{9}
Corpus Uteri	Herb. THC	25.436	5.293	1.70×10^{6}	4.16×10^{-6}	3.01×10^{-4}	6.37×10^{13}	2.03×10^{8}
Prostate	Herb. THC	24.791	5.498	7.03×10^{6}	1.65×10^{-5}	1.21×10^{-3}	9.35×10^{12}	2.98×10^{7}
Oesophagus	Herb. THC	13.982	3.228	1.58×10^{5}	3.58×10^{-5}	2.65×10^{-3}	3.05×10^{12}	9.59×10^{6}
Leukaemia—Lymphoid	LM. Cannabis: Herb. THC	7.397	3.030	1.57×10^{2}	2.59×10^{-2}	1.0000	2.60×10^{23}	7.91×10^{4}
Melanoma	Herb. THC	10.965	3.151	5.17×10^{4}	1.03×10^{-3}	7.76×10^{-2}	1.26×10^{10}	3.90×10^{4}
Cervix	Herb. THC	13.081	5.359	1.48×10^{2}	2.46×10^{-2}	1.00	1.47×10^{7}	45.71
Oesophagus	Resin. THC	1.763	0.155	1.11×10^{-28}	1.27×10^{-27}	3.04×10^{-26}	68.18	36.84
All Cancers nNMSC	Tobacco: Herb. THC	0.527	0.059	9.85×10^{-19}	5.87×10^{-18}	2.45×10^{-16}	48.59	23.92
Oropharynx	Income	1.024	0.191	3.81×10^{-7}	1.01×10^{-6}	7.12×10^{5}	67.24	18.20
Stomach	LM. Cannabis	1.283	0.096	3.16×10^{-38}	6.28×10^{-37}	8.98×10^{-36}	13.60	10.06
Kidney	Herb. THC	6.010	2.758	2.95×10^{-2}	4.60×10^{-2}	1.00	2.69×10^{6}	7.94
Colorectum	LM. Cannabis	1.323	0.115	2.41×10^{-29}	3.27×10^{-28}	6.69×10^{-27}	10.26	7.56
Myeloma	Resin. THC	0.526	0.090	6.60×10^{-9}	2.12×10^{-8}	1.36×10^{-6}	14.34	7.06
Ovary	Herb. THC	9.381	4.345	3.10×10^{-2}	4.76×10^{-2}	1.00	2.37×10^{6}	6.91
Larynx	Resin. THC	0.796	0.145	4.56×10^{-8}	1.33×10^{-7}	8.99×10^{-6}	10.56	5.48
Larynx	LM. Cannabis	0.612	0.068	8.34×10^{-19}	5.08×10^{-18}	2.09×10^{-16}	6.93	5.05
Leukaemia—Lymphoid	Alcohol	0.164	0.021	4.81×10^{-13}	2.24×10^{-12}	1.13×10^{-10}	5.96	4.29
Breast	LM. Cannabis	0.628	0.086	3.61×10^{-13}	1.71×10^{-12}	8.51×10^{-11}	5.32	3.83
Thyroid	LM. Cannabis	0.433	0.065	4.51×10^{-11}	1.75×10^{-10}	1.00×10^{-8}	5.07	3.57
Pancreas	Herb. THC	5.546	2.709	4.09×10^{-2}	6.06×10^{-2}	1.00	1.14×10^{6}	3.00
Hodgkin's	LM. Cannabis	0.253	0.044	1.54×10^{-8}	4.64×10^{-8}	3.08×10^{-6}	4.28	2.98
Gallbladder and Biliary	Tobacco: LM. Cannabis: Herb. THC	0.266	0.034	7.85×10^{-15}	4.10×10^{-14}	1.90×10^{-12}	3.72	2.95
Leukaemia—Myeloid	LM. Cannabis: Herb. THC	10.783	5.449	4.96×10^{-2}	7.24×10^{-2}	1.00	1.08×10^{19}	2.67

Table 10. *Cont.*

Cancer	Term	β-Estimate	Std. Error	*p*-Value	Adj. P. FDR	Adj. P. Holm	E-Value Estimate	E-Value 95% Lower Bound
Oropharynx	Tobacco: Herb. THC	0.509	0.187	7.31×10^{-3}	1.27×10^{-2}	9.36×10^{-1}	11.00	2.66
Leukaemia—Myeloid	Alcohol	0.195	0.037	6.00×10^{-7}	1.53×10^{-6}	1.09×10^{-4}	3.78	2.63
Corpus Uteri	LM. Cannabis	0.611	0.120	3.94×10^{-7}	1.04×10^{-6}	7.34×10^{-5}	3.64	2.55
Gallbladder and Biliary	LM. Cannabis	0.252	0.055	5.50×10^{-6}	1.31×10^{-5}	9.57×104	3.55	2.40
Colorectum	Tobacco: LM. Cannabis: Herb. THC	0.453	0.069	5.71×10^{-11}	2.18×10^{-10}	1.26×10^{-8}	2.96	2.37
Myeloma	Income	0.137	0.023	6.68×10^{-9}	2.12×10^{-8}	1.37×10^{-6}	2.77	2.19
Testis	Income	0.440	0.076	7.35×10^{-9}	2.28×10^{-8}	1.49×10^{-6}	2.76	2.18
Prostate	LM. Cannabis	0.512	0.125	4.20×10^{-5}	9.14×10^{-5}	6.81×10^{-3}	3.05	2.08
Prostate	Income	0.372	0.054	9.01×10^{-12}	3.63×10^{-11}	2.03×10^{-9}	2.47	2.08
Stomach	Tobacco: LM. Cannabis: Herb. THC	0.317	0.058	4.27×10^{-8}	1.26×10^{-7}	8.46×10^{-6}	2.63	2.07
Thyroid	Tobacco: LM. Cannabis: Herb. THC	0.202	0.038	9.80×10^{-8}	2.73×10^{-7}	1.88×10^{-5}	2.62	2.06
All Cancers	Alcohol	0.092	0.013	5.34×10^{-13}	2.45×10^{-12}	1.25×10^{-10}	2.36	2.03
Oropharynx	Tobacco	0.148	0.033	1.44×10^{-5}	3.27×10^{-5}	2.42×10^{-3}	2.71	2.00
Breast	Tobacco: LM. Cannabis: Herb. THC	0.267	0.051	1.98×10^{-7}	5.47×10^{-7}	3.78×10^{-5}	2.54	2.00
Anus	Tobacco: LM. Cannabis: Herb. THC	0.138	0.027	4.91×10^{-7}	1.26×10^{-6}	8.99×10^{-5}	2.55	1.98
Breast	Income	0.216	0.037	8.22×10^{-9}	2.53×10^{-8}	1.66×10^{-6}	2.25	1.87
Non-Hodgkin's Lymphoma	Tobacco: Herb. THC	0.314	0.103	2.26×10^{-3}	4.19×10^{-3}	3.12×10^{-1}	3.15	1.82
Lung	Tobacco: Herb. THC	0.186	0.061	2.51×10^{-3}	4.62×10^{-3}	3.44×10^{-1}	3.11	1.80
Brain	Income	0.136	0.027	7.04×10^{-7}	1.76×10^{-6}	1.27×10^{-4}	2.09	1.72
Gallbladder and Biliary	Tobacco	0.072	0.005	1.16×10^{-41}	2.89×10^{-40}	3.34×10^{-39}	1.76	1.68
Larynx	Alcohol	0.097	0.010	8.57×10^{-22}	6.38×10^{-21}	2.22×10^{-19}	1.76	1.64
Colorectum	Resin. THC	0.604	0.242	1.28×10^{-2}	2.14×10^{-2}	1.00	3.74	1.64
Prostate	Tobacco: LM. Cannabis: Herb. THC	0.253	0.074	6.94×10^{-4}	1.37×10^{-3}	1.03×10^{-1}	2.03	1.53
Kidney	Tobacco: LM. Cannabis: Herb. THC	0.127	0.037	7.28×10^{-4}	1.43×10^{-3}	1.07×10^{-1}	2.03	1.52
Colorectum	Tobacco	0.104	0.007	1.16×10^{-46}	4.95×10^{-45}	3.39×10^{-44}	1.54	1.49
Breast	Tobacco	0.074	0.005	5.07×10^{-43}	1.51×10^{-41}	1.47×10^{-40}	1.53	1.47
Oesophagus	Tobacco: LM. Cannabis: Herb. THC	0.136	0.044	1.86×10^{-3}	3.48×10^{-3}	2.60×10^{-1}	1.96	1.45
Stomach	Tobacco	0.076	0.006	3.92×10^{-37}	6.88×10^{-36}	1.11×10^{-34}	1.50	1.44

Table 10. *Cont.*

Cancer	Term	β-Estimate	Std. Error	*p*-Value	Adj. P. FDR	Adj. P. Holm	E-Value Estimate	E-Value 95% Lower Bound
Colorectum	Alcohol	0.103	0.017	7.58×10^{-10}	2.66×10^{-9}	1.62×10^{-7}	1.54	1.41
Pancreas	Tobacco: LM. Cannabis: Herb. THC	0.108	0.037	3.44×10^{-3}	6.22×10^{-3}	4.62×10^{-1}	1.91	1.40
Ovary	LM. Cannabis	0.249	0.099	1.16×10^{-2}	1.97×10^{-2}	1.00	2.26	1.40
Corpus Uteri	Tobacco	0.077	0.007	1.75×10^{-25}	1.58×10^{-24}	4.66×10^{-23}	1.43	1.37
Oropharynx	Tobacco: LM. Cannabis	0.060	0.020	2.75×10^{-3}	5.02×10^{-3}	3.74×10^{-1}	1.76	1.37
All Cancers nNMSC	Tobacco: LM. Cannabis	0.014	0.001	1.10×10^{-28}	1.27×10^{-27}	3.01×10^{-26}	1.41	1.36
Ovary	Tobacco	0.056	0.006	3.11×10^{-20}	2.21×10^{-19}	8.00×10^{-18}	1.39	1.34
Prostate	Tobacco	0.068	0.008	7.41×10^{-19}	4.60×10^{-18}	1.86×10^{-16}	1.38	1.33
Corpus Uteri	Tobacco: LM. Cannabis: Herb. THC	0.188	0.072	0.0085	0.0147	1.0000	1.83	1.32
Hodgkin's	Tobacco: LM. Cannabis: Herb. THC	0.067	0.026	0.0091	0.0157	1.0000	1.84	1.31
Bladder	Resin. THC	0.266	0.125	0.0330	0.0505	1.0000	3.30	1.30
Testis	Tobacco	0.063	0.009	2.70×10^{-11}	1.06×10^{-10}	6.02×10^{-9}	1.37	1.29
Prostate	Alcohol	0.075	0.018	3.02×10^{-5}	6.71×10^{-5}	0.0050	1.41	1.27
Oesophagus	Alcohol	0.041	0.011	1.26×10^{-4}	2.63×10^{-4}	0.0198	1.39	1.25
Stomach	Alcohol	0.053	0.014	1.41×10^{-4}	2.92×10^{-4}	0.0219	1.39	1.25
Oropharynx_Broad	Tobacco	0.037	0.012	0.0017	0.0033	0.2432	1.42	1.23
Larynx	Tobacco	0.024	0.004	9.70×10^{-9}	2.95×10^{-8}	1.95×10^{-6}	1.29	1.22
Melanoma	Tobacco: LM. Cannabis	0.020	0.002	4.91×10^{-18}	2.87×10^{-17}	1.22×10^{-15}	1.25	1.22
Liver	Tobacco: LM. Cannabis	0.018	0.002	3.69×10^{-16}	2.03×10^{-15}	9.03×10^{-14}	1.25	1.21
Cervix	Alcohol	0.059	0.018	0.0008	0.0016	0.1181	1.36	1.21
Breast	Alcohol	0.041	0.012	0.0011	0.0020	0.1510	1.35	1.20
Lung	Tobacco: LM. Cannabis	0.011	0.001	5.55×10^{-15}	2.95×10^{-14}	1.35×10^{-12}	1.23	1.20
Melanoma	Income	0.073	0.031	0.0183	0.0297	1.0000	1.60	1.19
Bladder	LM. Cannabis	0.126	0.059	0.0332	0.0505	1.0000	2.08	1.19
Pancreas	Tobacco: LM. Cannabis	0.014	0.002	1.62×10^{-12}	7.01×10^{-12}	3.73×10^{-10}	1.22	1.18
Melanoma	Tobacco: LM. Cannabis: Herb. THC	0.095	0.043	0.0266	0.0420	1.0000	1.73	1.18
Oesophagus	Tobacco: LM. Cannabis	0.015	0.002	7.62×10^{-11}	2.80×10^{-10}	1.67×10^{-8}	1.21	1.17
Kidney	Tobacco: LM. Cannabis	0.013	0.002	2.33×10^{-10}	8.48×10^{-10}	5.07×10^{-8}	1.21	1.17
Brain	Tobacco: LM. Cannabis: Herb. THC	0.081	0.038	0.0308	0.0476	1.0000	1.71	1.15
Thyroid	Alcohol	0.027	0.011	0.0156	0.0258	1.0000	1.33	1.12

Table 10. *Cont.*

Cancer	Term	β-Estimate	Std. Error	*p*-Value	Adj. P. FDR	Adj. P. Holm	E-Value Estimate	E-Value 95% Lower Bound
Anus	Tobacco: LM. Cannabis	0.006	0.001	6.92×10^{-5}	0.0001	0.0110	1.16	1.11
Non-Hodgkin's Lymphoma	Tobacco: LM. Cannabis	0.009	0.002	6.70×10^{-5}	0.0001	0.0107	1.16	1.11
Testis	Tobacco: LM. Cannabis: Herb. THC	0.154	0.076	0.0422	0.0619	1.0000	1.69	1.09
All Cancers	Tobacco: LM. Cannabis	0.013	0.006	0.0307	0.0476	1.0000	1.31	1.08
Cervix	Tobacco	0.017	0.007	0.0192	0.0310	1.0000	1.17	1.06

Table key: β-Estimate—estimate of the regression coefficient; Std. Error—standard error of the regression coefficient; *p*-value—significance level; P. Adj. Holm—*p*-value adjusted for multiple testing by the method of Holm; Adj. P. FDR—*p*-value adjusted for multiple testing by the false discovery rate method of Benjamini and Hochberg; E-value—expected value required of some unknown confounder covariate with both the exposure and the outcome to explain the observed effect; lower bound of the E-value—the 95% lower bound of the confidence interval of the E-value.

3.3.3. Multivariable Conclusions

The above results demonstrate that in these fixed-effects and panel multivariable regression models, the impact of cannabis is greater than that of the other covariates. A major remaining issue is how each of the different cancers assessed performed across the various models. This issue is addressed in Table 12, which sets out the six different multivariable models and considers only those cancers which were shown to be significant after adjustment for multiple testing (by the Holm's method).

Table 11. Summary of significant positive terms from interactive panel regression.

Term	Count	Negative Total of *p*-Value Exponents	Mean of the Negative *p*-Value Exponents	Median of the Negative *p*-Value Exponents	Total of the Lower E-Value Exponents	Mean of the Lower E-Value Exponents	Median of the Lower E-Value Exponents
Herb. THC	17	128	7.53	7	174	10.24	11
Resin. THC	6	60	10.00	7.5	10	1.67	0
Herb. THC: Resin. THC	2	2	1.00	1	4	2.00	2
Income	7	48	6.86	8	1	0.14	0
Last Month's Cannabis	11	124	11.27	7	1	0.09	0
Tobacco: Herb. THC	4	24	6.00	2	1	0.25	0
Alcohol	11	76	6.91	4	0	0	0
Tobacco	12	254	21.17	18.5	0	0	0
Tobacco: Last Month's Cann.	11	115	10.45	10	0	0	0
Tobacco: LM. Cann: Herb. THC	15	67	4.47	3	0	0	0

Table key: Term—relates to the number of models which include the cited independent covariate as significant. The other columns in this table relate to the described parameters.

Appendix B

DRUG FREE AUSTRALIA

DRUG FREE AUSTRALIA'S SUMMARY

OF THE US NATIONAL INSTITUTES OF HEALTH

2017 REVIEW

"THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS"

This summary is to facilitate the Australian public's understanding of the harms or benefits of cannabis, particularly in light of the spread of inaccurate information about the usefulness of medicinal cannabis, and in light of the push for cannabis legalisation.

From page v & vi of the NIH report

COMMITTEE ON THE HEALTH EFFECTS OF MARIJUANA: AN EVIDENCE REVIEW AND RESEARCH AGENDA

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Eric Bass, Johns Hopkins University
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Eric B. Larson**, Group Health Research Institute, and **Bobbie A. Berkowitz**, Columbia University Medical Center. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (p. 8). The National Academies Press. Kindle Edition.

MEDICINAL CANNABIS – National Institutes of Health 2017 Conclusions

National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. The National Academies Press. Kindle Edition

There is conclusive or substantial evidence that cannabis or cannabinoids are effective for:

Condition	Research	Mode of administration	Limitations
Chronic pain (4-1)	5 reviews 2 additional studies	22 studies plant based cannabinoids (13 x nabiximols, 5 x plant flower, 3 x oramucosal spray, 1 x oral THC, 5 x synthetic THC nabilone	"It is worth noting that the conclusions across all the reviews were largely consistent in suggesting that cannabinoids demonstrate a modest effect on pain."
Antiemetics in the treatment of chemotherapy-induced nausea and vomiting (4-3)	3 reviews	Nabilone Tetrahydrocannabinol Levantradol Dronabinol Nabiximols	Nabilone and dronabinol "were both found to be superior to placebo and equivalent to antiemetics at the time." (1980s) "Dronabinol equivalent to ondansetron . . . although no comparison to the currently more widely used neurokinin-1 inhibitors has been conducted."
multiple sclerosis spasticity symptoms (4-7a)	2 reviews, 1 additional study	Oral cannabis extract Nabiximols Orally administered THC	"The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale."

There is moderate evidence that cannabis or cannabinoids are effective

Condition	Research	Mode of administration	Limitations
Improving **short-term sleep outcomes** in individuals with sleep	1 review	Nabilone Dronabinol Nabiximols	There was only one comparison study against something other than placebo, amitriptyline, which is a second-line treatment when there is "availability of newer, more effective treatments

disturbance associated with **obstructive sleep apnea syndrome**, **fibromyalgia, chronic pain, and multiple sclerosis** (4-19)		THC/CBD capsules Smoked THC	that have fewer adverse effects."

There is moderate evidence of a statistical association between cannabis smoking

Condition	Research	Mode of administration	Limitations
Improved airway dynamics with acute use, but not with chronic use (7-1a)	1 review various additional studies	Smoked cannabis	"Overall, acute cannabis use was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly." "While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology."
Higher forced vital capacity (FVC) (7-1b)	1 review various additional studies	Smoked cannabis	"Overall, acute cannabis use was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly." "While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology."
Better cognitive performance among individuals **with psychotic disorders** and a history of cannabis use (12-2a)	3 reviews	Cannabis use	"Overall, the totality of data favor the conclusion that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders. It is not clear how the difference in scores might translate with respect to overall improved outcomes in functioning beyond the test setting. Furthermore, other data do not support the notion that acute cannabis exposure improves cognitive performance in patients

			with psychotic disorders, as acute intoxication is associated with impaired cognitive performance in cognitive domains of memory, learning, and attention."

There is limited evidence that cannabis or cannabinoids are effective

Condition	Research	Mode of administration	Limitations
Increasing appetite and decreasing weight loss associated with HIV/AIDS (4-4a)	2 reviews	Dronabinol Inhaled cannabis	"There have not been any randomized controlled trials conducted studying the effect of plant-derived cannabis on appetite and weight with weight as the primary endpoint. This is, in part, due to existing obstacles to investigating the potential therapeutic benefit of the cannabis plant."
Improving clinician-measured **multiple sclerosis spasticity symptoms** (4-7a)	2 reviews 1 additional study	Nabiximols Nabilone Oral THC/CBD Oral cannabis extract	"The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices such as the modified Ashworth scale in patients with MS."
Improving symptoms of **Tourette syndrome** (4-8)	2 reviews 2 additional studies with 4 reports	THC capsules	"However, case reports have suggested that cannabis can reduce tics and that the therapeutic effects of cannabis might be due to the anxiety-reducing properties of marijuana rather than to a specific anti-tic effect."
Improving **anxiety symptoms**, as assessed by a public speaking test, in individuals with social anxiety disorders (4-17)	1 review	CBD	"These positive findings are limited by weaknesses in the study design (e.g., an inadequate description of randomization and allocation concealment), a single dose of CBD, and uncertain applicability to patients with other anxiety disorders. Limited evidence also suggests short-term benefits in patients with chronic pain and associated anxiety symptoms. In contrast, evidence from observational studies found moderate evidence that daily cannabis use is associated with increased anxiety

			symptoms and heavy cannabis use is associated with social phobia disorder."
Improving symptoms of **posttraumatic stress disorder** (4-20)	1 study Extra studies in process	Nabilone	"Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment period."

There is limited evidence of a statistical association between cannabinoids

Condition	Research	Mode of administration	Limitations
Better outcomes (i.e., mortality, disability) after a **traumatic brain injury or intracranial hemorrhage** (4-15)	2 studies	Cannabis use – not otherwise stated	". . . more conclusive observational studies or randomized controlled trials will be necessary before any conclusions can be drawn about the neuroprotective effect of cannabinoids in clinical populations."
A **decrease** in the production of several **inflammatory cytokines** in healthy individuals (8-1a) smoked cannabis	4 studies	Cannabis use Dronabinol	"The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence."

There is limited evidence that cannabis or cannabinoids are ineffective

Condition	Research	Mode of administration	Limitations
Improving symptoms associated with **dementia** (4-13)	2 reviews 1 additional study	Dronabinol Oral THC	

Improving intraocular pressure associated with **glaucoma** (4-14)	1 review	THC oromucosal spray CBD oromucosal spray	"The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure must provide continual rather than transient reductions in intraocular pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours), suggesting a limited potential for cannabinoids in the treatment of glaucoma."
Reducing **depressive symptoms** in individuals with chronic pain or multiple sclerosis (4-18)	1 review	Nabiximols Dronabinal Nabilone	Although patients report using cannabinoids for depression, our search for a good-quality systematic review did not identify any RCTs evaluating the effects of medical cannabis in patients with depressive disorders. Trials in patients with chronic pain or multiple sclerosis with uncertain baseline depressive symptoms did not show an effect. There are no trial data addressing the effects of cannabinoids for major depressive disorder."

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment

Condition	Research	Mode of administration	Limitations
Cancers, including glioma (4-2)	1 review	No extra studies beyond the one review	"The review focused exclusively on the anti-tumor effects of cannabinoids on gliomas." "The signal from the preclinical literature suggests that clinical research with cannabinoids needs to be conducted."
Cancer-associated **anorexia cachexia syndrome and anorbnexia nervosa** (4-4b)	3 studies	Cannabis extract THC	"Increased appetite was reported by 73 percent of the cannabis-extract, 58 percent of the THC group, and 69 percent of the placebo recipients." "Megestrol acetate was superior to dronabinol for the improvement of both appetite and weight, with the combination therapy conferring no additional benefit."

Symptoms of **irritable bowel syndrome** (4-5)	1 study	Dronabinol	"The quality of evidence for the finding of no effect for irritable bowel syndrome is insufficient based on the short treatment duration, small sample size, short-term follow-up, and lack of patient-reported outcomes."
Epilepsy (4-6)	2 reviews 2 case series	CBD CBD/THC	"Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence of efficacy."
Spasticity in patients with paralysis due to **spinal cord injury** (4-7b)	2 reviews 1 additional study	Nabiximols Nabilone Oral THC Oral THC/CBD	"Given the lack of published papers reporting the results of trials conducted in patients with spasticity due to spinal cord injury, there is insufficient evidence to conclude that cannabinoids are effective for treating spasticity in this population."
Symptoms associated with **amyotrophic lateral sclerosis** (4-9)	1 study	Dronabinol	"Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated."
Chorea and certain neuropsychiatric symptoms associated with **Huntington's disease** (4-10)	1 review	Nabilone CBD	"Both studies were of short duration and likely underpowered because of their small sample sizes."
Motor system symptoms associated with **Parkinson's disease or the levodopa-induced**	1 review 2 studies	THC/CBD Nabilone CBD Smoked cannabis	"Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven-patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample

dyskinesia (4-11)			size limits the interpretation of the data. An observational study of inhaled cannabis demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations."
Dystonia (4-12)	1 review 1 additional study	Dronabinol Nabilone	"Two small trials of dronabinol and nabilone failed to demonstrate a significant benefit of the cannabinoids in improving dystonia compared with placebo. Cannabis has not been studied in the treatment of dystonia. Cannabis has not been studied in the treatment of dystonia."
Achieving **abstinence** in the use of addictive substances (4-16)	2 reviews	Dronabinol Nabiximols Inhaled CBD	"Based on the systematic reviews, neither of the two trials evaluating the efficacy of a cannabinoid in achieving or sustaining abstinence from cannabis showed a statistically significant effect. However, given the limited number of studies and their small size, their findings do not definitively rule out the existence of an effect."
Mental health outcomes in individuals with **schizophrenia or schizophreniform psychosis** (4-21)	2 reviews	CBD	"These studies provide only limited evidence due to the risk of bias, the short-term follow-up, and the evaluation of a single cannabinoid. Furthermore, the larger trial was designed to detect a moderate benefit of cannabidiol compared to the antipsychotic amisulpride, but it enrolled only 60 percent of the planned sample. Thus, it did not have the statistical power to detect small or moderate differences between CBD and amisulpride."

There is substantial evidence of a statistical association

Condition	Research	Mode of administration	Limitations
cannabis smoking and **worse respiratory**	1 review 5 additional studies	Cannabis smoking	"Cannabis smoking cessation was temporally associated with the resolution of chronic bronchitis symptoms, and a small

symptoms and more **frequent chronic bronchitis** episodes (7-3a)			feasibility study suggests that use of a vaporizer instead of smoking cannabis may lead to the resolution of respiratory symptoms."
Increased risk of **motor vehicle crashes** (9-3)	6 reviews	Cannabis use	"A missing component in this review (, Rogeberg and Elvik (2016)) is a better determination of the dose at which driving becomes sufficiently unsafe as to increase MVC risk."
Lower birth weight of the offspring – maternal smoking (10-2)	1 review 10 additional studies	Cannabis use	"The findings for birth weight are consistent with the effects of non-cannabinoid substances in smoked cannabis and cigarette smoking. It has been shown in several studies that the increases in carbon monoxide, with elevated carboxyhemoglobin blood levels, may be up to fivefold higher after marijuana than cigarettes.1'
The development of **schizophrenia** or other psychoses, with the highest risk among the most frequent users (12-1)	5 reviews 4 additional studies	Cannabis use	"The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors."
Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is **not a risk factor** for the development of problem cannabis use (13-2e)	1 review	Cannabis ever used Cannabis dependence	"One significant limitation of any conclusions drawn from the current literature is that the data on cannabis use, other drug use, and the symptoms of problem cannabis use are derived from self-reports."

Being male and smoking cigarettes are **risk factors** for the progression of cannabis use to problem cannabis use (13-2i)	Data from NLAES Data from NLSAH Data from NHSDA	Cannabis dependence	
Initiating **cannabis use at an earlier age** is a **risk factor** for the development of problem cannabis use (13-2j)	4 studies	Cannabis dependence	
Increases in cannabis use frequency and the progression to developing **problem cannabis use** (13-1)	5 studies	Cannabis dependence	"The limitations of these studies include the reliance on self-reported cannabis use, the fact that data were restricted to two time points of assessment separated by 3 years, and that the findings are based on epidemiological data obtained more than 10 years ago. A significant issue with relying on self-report methodologies to ascertain problem cannabis use is that this requires that the respondent have insight into the fact that cannabis is actually causing problems in order to meet criteria for cannabis abuse/dependence (as per the DSM-IV) or CUD (as per the DSM-V)."
Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)	4 studies	Cannabis dependence	

There is moderate evidence of/ or there is a statistical association between cannabis use

Condition	Research	Mode of administration	Limitations/Other
Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)	10 studies	Cannabis use including edible	"Collectively, these findings indicate that state-based legalization of cannabis is associated with a subsequent increase in pediatric cannabis exposures in those states." "Data from poison centers will capture only the subset of cannabis-related overdose injuries or deaths that resulted in a call to a poison center and may over-represent serious cases or cases from states where cannabis is legal."
The **impairment in the cognitive domains of learning, memory, and attention** (11-1a)	Learning - 3 reviews memory - 3 reviews cognition - 4 reviews	Cannabis use	
Increased symptoms of **mania and hypomania** in individuals diagnosed with bipolar disorders (12-4)	1 review 2 additional studies	Cannabis use	"Many of these studies do not take into account the variance among the subtypes of cannabis or in the potency or route of administration, all of which could lead to difference in results. Also, the lack of precision in measuring the frequency of cannabis use at baseline and in measuring follow-up data remains a problem."
A small increased risk for the development of **depressive disorders** (12-5)	2 reviews, 7 additional studies	Cannabis use	"Although the supplemental studies from the primary literature reported mixed findings, the committee concludes that there is a strong enough evidence base to support the conclusion that there is an association between cannabis use and a small increased risk (pOR of 1.17; Lev-Ran et al., 2013) of developing depressive disorders, which increases with increased frequency of use (OR of 1.62;"
Increased incidence of **suicidal ideation** and suicide attempts with a	2 reviews one additional study	Cannabis use	"The studies presented demonstrate evidence of a dose–response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicidal attempts."

higher incidence among heavier users (12-7a)			"Several limitations should be noted, including the lack of homogeneity in the measurement of cannabis exposure, the lack of systematic controls for known risk factors, the short period of observation for suicidality, the variability in the covariates used to adjust for confounders, the differences in the dose–response analyses, and problems of small sample size."
Increased incidence of suicide completion (12-7b)	2 reviews 1 additional study	Cannabis use	"However, there are several limitations, including that suicidality was only assessed in participants who reported a 2-week period of depressed mood or anhedonia, so the results might underestimate the effect for those that have suicidal ideation or suicide attempts without these symptoms."
Increased incidence of social anxiety disorder (12-8b)	1 review 8 additional studies	Cannabis use	"Some of the limitations of these studies are that cannabis use was ascertained by self-report; that causality cannot be established because of the possibility of residual confounding; that the follow-up period was limited to 3 years; and that there was a high loss in the follow-up and limited power to detect small effects.
Anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use (13-2b)	Anxiety - 1 review Psychopathology – 5 studies	Cannabis use	"It is important to highlight that the studies reviewed above vary in their age grouping and generally include populations that cross from late adolescence into young adulthood." "Another concern is that the structured interviews used to assess baseline dependent variables (i.e., mental health) and outcomes (i.e., problem cannabis use) vary between studies, and even for some longer longitudinal studies, within individual studies."
Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)	Psychopathology – 5 studies	Cannabis use	

Adolescent ADHD is not a risk factor for the development of problem cannabis use (13-2d)	1 review	Cannabis use	"Some suggestion of publication bias was noted, and heterogeneity was noted in the group of nine studies with data about marijuana abuse or dependence."
Being male is a risk factor for the development of **problem cannabis use** (13-2f)	4 studies	Cannabis use	"However, it is not known if differences between men and women would have emerged if a shorter time frame from cannabis use onset had been explored."
Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)	2 studies	Cannabis use	"The rate of developing cannabis dependence within 24 months of first cannabis use was doubled among respondents who had experience with three or more other drugs (tobacco, alcohol, and other drugs) prior to cannabis use (adjusted risk ratio [aRR] = 2.2; 95% CI = 1.1–4.3; p = 0.03)"
Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)	2 studies	Cannabis use	
During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental	9 studies	Cannabis use	

substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are **risk factors** for the development of problem cannabis use (13-2k)			
A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)	3 studies	Cannabis use	"In addition to the limitations cited for the first two sections such as issues with self-reported cannabis use, the respondents' reporting of symptoms of problem cannabis use, and data restricted to trends of cannabis use and cannabis strength that do not accurately reflect current trends, the current findings are additionally restricted to limited followup with participants and to only a few of the risk factors highlighted in the second section, including biological sex."
Problem cannabis use and **increased severity of posttraumatic stress disorder symptoms** (13-3c)	3 studies	Cannabis use	"It should be noted, however, that these are cross-sectional data and that the directionality and causality of these associations cannot be determined."
The **development of substance dependence** and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)	Alcohol – 2 studies Opioids – 1 study Tobacco – 1 study Mixed drug use – 3 studies		"With regard to alcohol use, cannabis users were found to be at a higher risk for heavy drinking than nonusers. With regard to opioids, cannabis use predicted continued opioid prescriptions 1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose–response relationships, and the

			potential for self-report bias."

There is moderate evidence of no statistical association between cannabis use

Condition	Research	Mode of administration	Limitations
Incidence of **lung cancer** (5-1)	1 review 1 additional study	Cannabis use	"Zhang et al. (2015) were unable to account for potential effect measure modifiers, including those related to variations in cannabis smoking techniques and in the characteristics of the cannabis smoked. The authors also noted that the small number of participants who were heavy and chronic cannabis users rendered effect estimates for these subgroups imprecise. Finally, the study relied on self-report without biological validation to assess patterns of cannabis, making it impossible to verify the accuracy of cannabis use data. Regarding Callaghan et al. (2013), detailed information on cannabis and tobacco use before and after baseline was lacking; the study did not adjust or account for tobacco or cannabis during the 40-year follow-up period; the authors were unaware whether study participants mixed tobacco and cannabis; and the self-reporting process was not anonymized."
Incidence of **head and neck cancers** (5-2)	1 review	Cannabis use	"First, although a nonsignificant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer. The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods. Finally, differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use (e.g., frequency, duration, method) affect the risk of head and neck cancers."

Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)	3 studies	Cannabis use	"With regard to negative symptoms, the data reviewed were generally more homogenous, with most studies reporting either an absence of association between cannabis use and negative symptoms or else reduced negative symptoms in cannabis users."

There is limited evidence that/ or there is a statistical association between cannabis use

Condition	Research	Mode of administration	Limitations
Non-seminoma-type **testicular germ cell tumors** (5-3)	2 reviews	Cannabis use	"First, each of the three case-control studies informing the review relied on self-report without biological validation," "bias. Second, two of the studies reported response rates that were both low and unequal:" "Third, the high and growing prevalence of cannabis use in the general population may render the category "ever-smoker" uninformative," "A final limitation is that the studies informing the review did not all control for the same, potentially relevant confounders:"
The triggering of **acute myocardial infarction** (cannabis smoking) (6-1a)	3 reviews provided descriptive background 2 studies	Cannabis use	"Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use."
Ischemic stroke or subarachnoid hemorrhage (6-2)	5 studies	Cannabis use	"Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g., smoked, edible, etc.); the absence of information on dose, including accounting for the

			content of THC and other cannabinoids and potential additives or contaminants; and the lack of information on the total lifetime duration/dose of cannabis use."
Decreased risk of metabolic syndrome and **diabetes** (6-3a)	Metabolic syndrome -3 studies Diabetes – 3 studies	Cannabis use	"As noted earlier, these are counterintuitive findings because THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis."
Increased risk of prediabetes (6-3b)	1 study	Cannabis use	
An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (7-2a)	6 studies	Cannabis smoking	"Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users."
Pregnancy complications for the mother (10-1)	1 review 3 additional studies	Cannabis use	"Despite identifying one good- to fair-quality systematic review addressing pregnancy complications for the mother, the findings of the review must be interpreted with caution. The review relied on a primary literature that is limited in the number, quality, and rigor of the studies that have been carried out to date."
Admission of the infant to the **neonatal intensive care unit** (NICU) (10-3)	1 review 1 study	Cannabis use	"Findings related to health care use, such as the increase in NICU admissions, need to be treated with caution. This pattern may reflect protocols requiring admission of all infants whose mothers have a history of substance use in pregnancy or failed toxicological screens during labor, rather than the health of the infant per se, particularly as there appears to be no increase in length of neonatal stay.

Impaired academic achievement and education outcomes (11-2)	1 review 8 studies	Cannabis use	The NIH listed 9 limitations – too many to list here but available on p 280 of the report
Increased rates of **unemployment and/or low income** (11-3)	8 studies	Cannabis use	"Because employment status is not static, it is possible that the relationships may be cyclical (e.g., depending on context, unemployment could contribute to the use of cannabis and other substances [Lee et al., 2015a] and cannabis/substance use could contribute to unemployment)."
Impaired social functioning or engagement in developmentally appropriate social roles (11-4)	1 review 4 studies	Cannabis use	"This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce selection bias; see Chassin et al., 2010). The use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative social outcomes."
An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)	2 reviews 7 additional studies	Cannabis use	"The limitations observed in the reviewed studies included variable adjustment for other drug use and baseline symptom severity; issues with study design (observational); a reliance on self-reports; and variable analyses of cannabis use (i.e., dose/amount/frequency, current versus lifetime)."
The likelihood of developing **bipolar disorder**, particularly among regular or daily users (12-3)	1 review 3 additional studies	Cannabis use	"Overall there is some evidence to support the association between cannabis use and the increased incidence of bipolar disorders. Although there is support for this association, more information is needed on the potential mediators that could explain the relationship as well as whether the risk is likely to occur only in conjunction with the use of other substances such as alcohol or nicotine.

The development of any type of **anxiety disorder**, except social anxiety disorder (12-8a)	1 review 8 additional studies	Cannabis use	"Further work needs to be done to examine why the outcomes differ depending on whether the assessment is done with anxiety symptoms or anxiety disorders and whether the explanatory variable is any cannabis use or cannabis use disorder."
Increased symptoms of **anxiety** (12-9)	1 study	Cannabis use	"In addition, although this study uses a prospective design in which cannabis use and temperament are evalutated at baseline to predict anxiety symptoms 1 year later, it is limited to college students (ages 18–21) in only one assessment site."
Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)	5 studies	Cannabis use	"Of the relevant studies reviewed, cannabis use appears to be associated with more severe symptoms, but limited sample sizes were an issue in certain studies; that issue, combined with the lack of adjustment for baseline symptom severity and other drug use and the examination of specialized patient populations, limits the strength of the conclusions that can be drawn."
Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use **(13-2a)**	Anxiety – 1 review 2 studies Depression – 3 studies	Cannabis use	
The **initiation of tobacco use** (14-1)	3 studies	Cannabis use	"Two studies had relatively large samples. The data do not provide compelling evidence that cannabis is associated with the initiation of other drugs of abuse, although this is one possibility."
Changes in the rates and **use patterns of other licit and illicit**	Alcohol – 1 study Opioids – 1 study Tobacco – 1 study	Cannabis use	"With regard to alcohol use, cannabis users were found to be at a higher risk for heavy drinking than nonusers. With regard to opioids, cannabis use predicted continued opioid prescriptions

substances (14-2)	Mixed drug use – 4 studies		1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose–response relationships, and the potential for self-report bias. “

There is no or insufficient evidence to support or refute a statistical association between cannabis use

Condition	Research	Mode of administration	Limitations
Incidence of **esophageal cancer** (5-4)	1 study	Cannabis use	“In conducting their investigation, Hashibe et al. (2006) addressed several methodological issues of previous studies of the association between cannabis use and cancer incidence. These issues included accounting for tobacco use and other confounders, avoiding measurement errors, and protecting the anonymity of participants.”
Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi’s sarcoma, or bladder cancer (5-5)	1 review 9 studies	Cannabis use	
Subsequent risk of developing acute myeloid leukemia/ acute non-	1 review	Cannabis use	

lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (5-6)			
Hospital admissions for COPD (7-2b)	1 study	Cannabis smoking	"Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users."
Asthma development or asthma exacerbation (7-4)	3 studies	Cannabis smoking	"The evidence linking cannabis use with asthma risk or exacerbation is limited by the scope and sample size of available studies and by the use of more standardized approaches to measure asthma prevalence or exacerbations of asthma."
Other **adverse immune cell responses** in healthy individuals (8-1b)	5 studies	Cannabis smoking	"The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence."
Adverse effects on immune status in individuals with HIV (8-2)	4 studies	Cannabis use	"However, each of the four studies possessed major shortcomings in experimental design which could have contributed to the absence of adverse effects being observed in HIV patients who used cannabis or cannabinoids; these shortcomings include study durations that where insufficient to observe adverse effects in the endpoints being measured, small numbers of study participants, and poorly defined and variable levels of cannabinoid exposure."
Increased incidence of oral human papilloma	2 studies	Cannabis use	

virus **(HPV)** (8-4)			
All-cause mortality (9-1)	3 reviews 2 additional studies	Cannabis use	"There is an overall dearth of cohort studies empirically assessing general population cannabis use and all-cause mortality. Although the available evidence suggests that cannabis use is not associated with an increased risk of all-cause mortality, the limited nature of that evidence makes it impossible to have confidence in these findings."
Occupational accidents or injuries (9-2)	9 studies	Cannabis use	"In light of the diversity among and limitations of these studies, it was not possible to determine whether general, nonmedical cannabis use is associated with a clearly increased risk of occupational accidents and injuries across a broad range of occupational and industrial settings in the absence of other important risk factors."
Death due to **cannabis overdose** (9-4a)	10 studies	Cannabis use	". . . Onders et al. (2016) observed that cannabis exposures are not identical to poisonings and overdoses; consequently, data on trends in cannabis exposures do not necessarily allow for an estimation of trends in cannabis overdose or poisoning."
Later outcomes in the offspring (e.g., **sudden infant death syndrome, cognition/academic achievement, and later substance use**) (10-4)	SIDS – 1 study Cognition/Academic Achievement - 6 studies Substance use – 5 studies	Cannabis smoking	"While the studies attempted to control for the child's environment using standard measures of socioeconomic status as well as a direct assessment of the home environment, these approaches may be insufficient to detect potentially subtle differences in the family and neighborhood environments of women who smoke cannabis during pregnancy and those who do not." "In addition, these studies did not address heritable or epigenetic vulnerability."
Changes in the course or symptoms of **depressive disorders**	No studies	Cannabis use	

(12-6)			
The **development of posttraumatic stress disorder** (12-10)	No studies	Cannabis use	

There is no evidence to support or refute a statistical association

Condition	Research	Mode of administration	Limitations
chronic effects of cannabis use and: The **increased risk of acute myocardial infarction** (6-1b)	3 reviews provided descriptive background 2 studies	Cannabis use	"Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use."

There is limited evidence of no statistical association between cannabis use and:

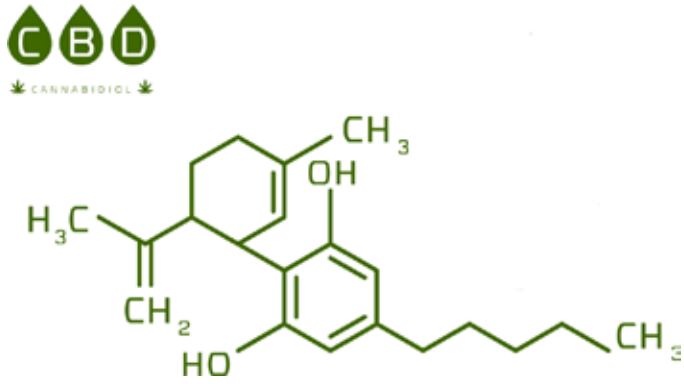
Condition	Research	Mode of administration	Limitations/Other
The progression of **liver fibrosis or hepatic disease** in individuals with viral hepatitis C (HCV) (8-3)	3 studies	Cannabis use	"Overall, the available evidence that cannabis use is not associated with the progression of liver fibrosis and hepatic disease in individuals with HCV is stronger than the available evidence that cannabis use is associated with the progression of liver fibrosis and hepatic disease in individuals with HCV."

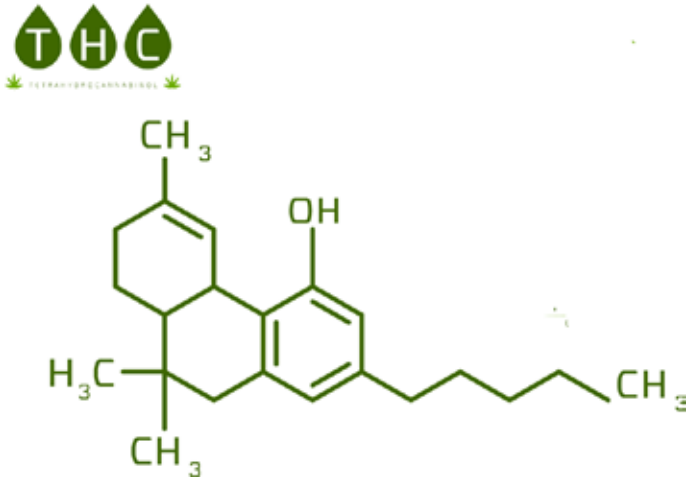
Appendix C

Missouri Medicine

The Journal of the Missouri State Medical Association www.msma.org/missouri-medicine September/October 2020

National Cannabis Review: Are CBD & THC Valid Medicines?

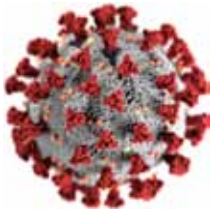




ATSU | A.T. Still University

FIRST IN WHOLE PERSON HEALTHCARE

FACULTY RESEARCH UPDATE



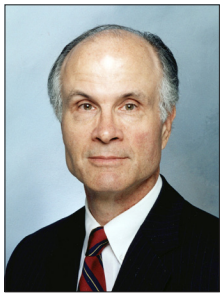
COVID-19 REPORT: Testing & Physician Wellness

Medical Fraud, Mislabeling, Contamination: All Common in CBD Products

by David G. Evans, JD

Cannabidiol (CBD) is an oil derived from the cannabis plant. It is touted as a "wonder drug." Advertisements claim it is perfectly safe and legal and can be used for all that ails you or makes you uncomfortable mentally or physically. People are consuming it under the misapprehension that it is safe, however, CBD has negative side effects and may interfere with the functioning of other medications and may be contaminated.

Consumer demand for CBD has increased due to aggressive marketing and fraudulent health claims. In the rush to market CBD, there has been little consideration of the concerns that must be addressed before CBD is given full acceptance. This article will explore those concerns.



David G. Evans, JD, is a graduate of Westminster College in Fulton, Missouri, and Rutgers Law School. He is Senior Counsel for the Cannabis Industry Victims Educating Litigators (CIVEL). CIVEL educates lawyers on the legal rights of the victims of the marijuana industry. He was formerly a Research Scientist in the New Jersey Department of Health.

Is CBD Legal?

There are claims that CBD from hemp used as a medicine or food is always legal. This is not accurate. The Agriculture Improvement Act of 2018 changed federal law regarding the production and marketing of hemp. Hemp is defined as cannabis and its derivatives with extremely low (less than 0.3% a dry weight basis) concentration of the THC. These changes removed hemp from the federal Controlled Substances Act, which means that it will no longer be an illegal substance under federal law. However, Congress explicitly preserved the FDA's authority to regulate these products under the Federal Food, Drug, and Cosmetic Act and section 351 of the Public Health Service Act. These compounds are subject to the same requirements as FDA-regulated products containing any other substance regardless of the source of the substance. Cannabis products claiming in their marketing materials that they're intended for use in the diagnosis, cure, mitigation, treatment, or prevention of

diseases must go through the FDA drug approval process for human or animal use before they are legally marketed.[1]

As stated by the FDA Commissioner:

"Selling unapproved products with unsubstantiated therapeutic claims is not only a violation of the law, but also can put patients at risk, as these products have not been proven to be safe or effective. This deceptive marketing of unproven treatments raises significant public health concerns, as it may keep some patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases."[2]

CBD products that are not approved by the FDA and are sold as medicines, or as food, or cosmetics are "black-market" and are illegally trafficked and sold. This includes those sold in reputable stores, restaurants, and other places that don't have FDA approval to do so. Black-market CBD products have not been evaluated by the FDA to determine if they are safe as foods or effective or safe for any medical use, and if safe, what the proper dosage would be. In addition, they are not administered with any federally approved medical protocols as are prescription drugs and there may be no warnings for how they interact with other drugs, or whether they have dangerous side effects.[3]

A pure form of CBD is approved by the FDA as a medicine for two rare seizure disorders. Its approval was based on well-controlled FDA clinical trials. This is a purified form of CBD in a reliable dosage form and a reproducible route of delivery. Since it is manufactured according to FDA standards by a reliable company that has followed the rules, we can assume it is free from adulterants and contaminants. Its side effects and other clinical data are publicly available. This type of data is not provided by the black-market CBD products.[4]

There are a number of papers discussing the pros and cons of CBD as a medicine that can be viewed on the National Library of Medicine website at www.nlm.nih.gov. Some studies, notwithstanding their many deficiencies, provide some support for the hypothesis that CBD may exert some beneficial effects, but is has yet to be proven to be both effective and safe. FDA quality studies with purified CBD are warranted. However, clinical data does not support some claimed uses of CBD for Parkinson's disease, schizophrenia, cancer palliation and treatment, chronic pain and spasticity, depression, anxiety disorder, insomnia, and inflammation. There is insufficient evidence to rate effectiveness of CBD for Bipolar disorder, Crohn's disease, diabetes, dystonia, Huntington's disease, multiple sclerosis (and its muscle spasms, tiredness, bladder control, the ability to move around, or well-being and quality of life), schizophrenia, nerve damage in the hands and feet (peripheral neuropathy) and other conditions.[5]

CBD Mislabeling and Contamination

Studies suggest that black-market CBD is not very reliable or safe. In 2020, the FDA did a study on products that claimed to have a specific amount of CBD and those claimed amounts were compared to the FDA testing results. Of the 102 products that indicated a specific amount of CBD, 18 products (18%) contained less than 80% of the amount of CBD indicated, 46 products (45%) contained CBD within 20 percent of the amount indicated, and 38 products (37%) contained more than 120 percent of the amount of CBD indicated. Of great concern is that 49% of the products tested contained THC.[6]

The *Journal of the American Medical Association* published a letter demonstrating the results of "undercover" purchases of CBD. Of 84 samples tested, THC was detected in 21%. There were other defects in the mislabeled products. Only 30.95% were accurately labeled. Accuracy of labeling depended on product type, with vaporization liquid most frequently mislabeled (87.50%) and oil most frequently labeled accurately (45.0 %). THC was detected (up to 6.43 mg/mL) in 18 of the 84 samples tested (21.43%).[7]

A Johns Hopkins researcher tested CBD products. Testing showed 44 products (59%) had detectible levels of CBD, but the average ratio of THC to CBD was 36-to-1. Only one product had a 1-to-1 ratio, which some research suggests is associated with fewer side effects and improved clinical benefit compared with higher ratios of THC to CBD. The testing indicated the edible cannabis products may have very little CBD.[8]

A study published by the National Institute of Health showed that products were mislabeled

with 26% containing less CBD than labeled and 43% containing more, indicating a high degree of variability and poor standardization of online products. Notably, the oil-based products were more likely to be accurate (45% compared to 25% for tincture and 12.5% for vaporization liquid) and had a smaller percentage of deviation. Oil based products also had a higher range of concentration. In addition to CBD mislabeling, THC was detected in 21% of samples. This study also notes that products containing THC could have sufficient enough concentrations to produce intoxication in children.[9]

In a recent federal lawsuit, the plaintiff bought CBD products relying on advertising that the products had "No Heavy Metals or Insecticides." The products failed laboratory testing for heavy metals, including copper, nickel, and lead and also for total yeast and mold. Lead can cause poisoning, speech, and language problems, neurologic toxicity, and reproductive problems. Mold can cause allergic and respiratory problems, and yeasts can cause infection in people with compromised immune systems.[10] On July 28, 2020, another CBD product was recalled due to lead contamination. The recall noted that acute lead poisoning could cause pain, muscle weakness, paresthesia, abdominal pain, nausea, vomiting, diarrhea, constipation, poor appetite, weight loss, symptoms associated with encephalitis, metallic taste in the mouth, shock, hemolysis, and kidney damage.[11]

False Medical Claims

Examples of false claims for CBD can be taken from FDA and Federal Trade Commission (FTC) warning letters to CBD companies. In order to make claims of treatment or medical use, products must obtain approval from the FDA after submitting their data. False claims include using CBD to treat: alcoholism, Alzheimer's disease, arthritis, autism, blood pressure and heart rate, cancer, chronic traumatic encephalopathy, cardiovascular disease, chemotherapy-induced hearing loss, colitis, concussions, depression, diabetes, leukemia, liver inflammation, lupus, Lyme disease, neurological damage, Parkinson's disease, stroke, schizophrenia, traumatic brain injury (TBI), and tumors.[12]

CBD Negative Side Effects and Drug Contraindications

There may be interactions between CBD and immunosuppressive drugs used in transplants or chemotherapy and with warfarin as there may be the potentiation of anticoagulant effects with marijuana, including CBD. CBD may interact with other medicines, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any cannabis-based products. CBD may affect the way other medicines work, and other medicines may affect how CBD works.

CBD may decrease how fast the liver metabolizes the drug. This may possibly increase the effects and side effects. CBD may potentially interact in a negative way with anti-epileptic drugs such as: carbamazepine (Tegretol), phenytoin (Dilantin), phenobarbital (Luminal, Solfoton, Tedral), primidone (anti-seizure). Users should be cautious before taking CBD with: sedatives, herbs, and supplements that cause drowsiness, seizure medications, drugs that are broken down and changed by the liver. People should be cautious with using Brivaracetam (Briviact), Eslicarbazepine (Aptiom), and Everolimus (Zostress).[13] Consumers should not take CBD with Clobazam for seizures.[14] The use of CBD along with these drugs might increase the effects and side effects of the drugs.

Adverse Reactions

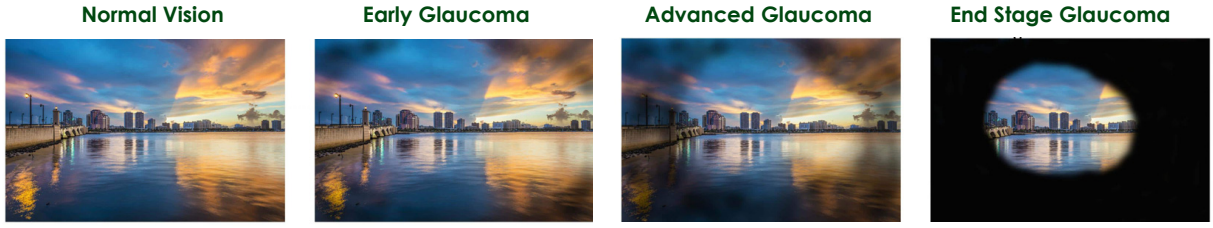
The adverse reactions to CBD include: hepatocellular injury, somnolence and sedation, suicidal behavior and ideation, hypersensitivity reactions–allergic reactions, negative interaction with anti-epilepsy drugs (such as Tegretol, Dilantin, luminal, Solfoton, Tedral, primidone), interactions with immunosuppressive drugs used in transplants or chemotherapy and with warfarin. CBD use can impair kidney function and cause anemia.[15] Black market CBD is generally sold without warnings about adverse reactions.

The side effects of CBD can include: drowsiness, decreased appetite, diarrhea, transaminase elevations, fatigue, feeling unwell (malaise), rash, difficulty sleeping (insomnia, disordered sleep, and poor-quality sleep), infections, somnolence, decreased appetite, diarrhea, and asthenia.[16]

Research shows that more than 40% of children with epilepsy who were given CBD orally had adverse events that included THC like symptoms. The research challenged the widely accepted premise that CBD is not intoxicating.[17]

Glaucoma Made Worse by Marijuana, THC, and CBD

by John C. Hagan III, Ophthalmologist Eye, MD



Source: https://www.graceandvision.com.au/eye-conditions/glaucoma/

Although glaucoma is a listed indication for issuing sham medical marijuana cards, the most recent evidence is that cannabis in either tetrahydrocannabinol (THC) or cannabidiol (CBD) are both harmful to the eye and have a deleterious effect on glaucoma.[1-5] CBD has been shown to increase intra-ocular pressure (IOP) the fundamental problem with most forms of glaucoma; while THC lowers IOP but the effect is transient and therapeutically worthless. Chronic cannabis use causes damage and loss of retina ganglion cells as does the disease glaucoma. Moreover, ganglion cells are central nervous system tissue, like the cells of the brain, and may serve as a surrogate marker for brain cell loss. This might account for neurological problems associated with heavy cannabis use such as memory loss, lethargy and poor motivation, permanent IQ loss in youthful users, aggression, psychosis, etc. Half a century of research has found no benefit to any cannabis products in ophthalmology. Use of sham medical marijuana, CBD or any form of cannabis is not recommended for glaucoma or any other eye condition by the American Academy of Ophthalmology or the Glaucoma Society. No physician should ever recommend cannabis use for any of the many forms of glaucoma.

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Glaucoma

A recent study suggests that CBD doesn't lower eye pressure but instead raises it. High eye pressure is the primary risk factor for glaucoma, a leading cause of blindness.[18] [Editor's Note: see sidebar.]

Warnings

Black Market CBD may be sold without warnings being provided. People should be warned about the known adverse reactions to CBD. People should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that CBD does not affect them adversely (e.g., impaired judgment, thinking, or motor skills). Use of CBD may increase the risk of suicidal thoughts and behavior. Hypersensitivity reactions can occur with use of CBD. It is not known if CBD is safe and effective in children under two years of age. FDA clinical trials of CBD did not include any patients aged above 55 years. CBD for elderly persons could be dangerous due to the greater frequency of decreased liver or cardiac function, and of concomitant disease or other drug therapy.[19]

Vehicle Operation

A recent FDA report states that CBD can cause sleepiness, sedation, and that may make operating a motor vehicle or machinery dangerous after consuming CBD products.[20]

CBD and Pregnancy

The FDA strongly advises that during pregnancy and while breastfeeding, women should not use CBD or THC. They may put themselves or their baby at serious risk by using these marijuana products. CBD products may also be contaminated with substances that may pose a risk to the fetus or breastfed baby such as pesticides, heavy metals, bacteria, and fungus. Studies in laboratory animals show male reproductive toxicity, including in the male offspring of CBD-treated pregnant females. This includes decrease in testicular size, inhibition of sperm development, and decreased testosterone.[21] The CDC also notes that marijuana use by a pregnant woman can have teratogenic effects causing birth defects.[22]

Drug Tests

CBD may affect drug test results. A truck driver lost his job when he tested positive for THC on a drug test after being told by the manufacturer that a CBD product had no THC.[23]

Recent CBD Lawsuits

There are many recent lawsuits filed against CBD manufacturers and more are on the way. They were filed after the FDA issued a series of warning letters that such products, unless approved by the FDA, are neither safe or effective for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or because they are intended to affect the structure or any function of the body. Some of the cases allege that the manufacturers' CBD products made false medical claims or were mislabeled as dietary supplements or there were false claims as to the amount of CBD present in the product. A California case claims that the company engaged in false and deceptive practices and that their products could not be sold legally. A Massachusetts case claimed that many of the defendant's products had significantly lower levels of CBD than advertised. A California case claimed that the defendant company made false claims that CBD could help the symptoms of autism and that could treat illnesses such as hepatitis, cancer, and Tourette syndrome. A New York case alleges false medical claims for marijuana and for violations of the federal securities laws. A Florida case alleged that CBD has "been touted as having numerous positive health effects." CBD has been used to treat conditions such as "anxiety, sleep disorders, and chronic pain." In selling the products with significantly less CBD, plaintiff claimed the Defendants "are cheating every consumer who buys the products by that amount." The Federal Trade Commission recently petitioned to enjoin a CBD company from disseminating false or unsubstantiated advertisement claims in connection sale of a product that purportedly treats, prevents or reduces the risk of COVID-19 and products that purportedly treat cancer.[24]

Government Bans on CBD Use

The federal Department of Transportation has issued a warning that CBD use can show up as a positive THC result on a drug test.[25] The U.S. military has banned the use of hemp/CBD products for military personnel.[26]

The Future of CBD and the FDA

The FDA is currently undertaking a large long-term study of black-market CBD products to understand the characteristics of CBD products in order to make informed decisions about how best to protect public health. The FDA will report again on the results from both the near and long-term studies when complete data sets are available.[27] On July 21, 2020, the FDA stated that in regard to CBD and other cannabinoids:

"The FDA believes the drug approval process represents the best way to ensure that safe and effective new medicines, including any drugs that contain cannabis or cannabis-derived compounds, are available to patients in need of appropriate medical therapy."[28]

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Disclosure

This article should not be considered legal or medical advice. This is for informational purposes only. Use of and access to these materials does not in itself create an attorney-client, or any professional relationship, between David G. Evans and CIVEL and the user or reader. Mr. Evans or CIVEL cannot vouch for any study cited herein since they did not do the study. The readers should consult the study and make their own interpretation as to its accuracy. Be advised that case law and statutory and regulatory laws cited herein may have been amended or changed by publication date. **MM**

COLORADO
Department of Revenue
Enforcement Division - Marijuana

Public Health and Safety Advisory

November 3, 2017 - In accordance with the Governor's Executive Order (D 2015-015), the Colorado Department of Revenue ("DOR"), in conjunction with the Colorado Department of Agriculture ("CDA") and the Colorado Department of Public Health and Environment ("CDPHE"), are issuing an immediate health and safety advisory due to the identification of potentially unsafe pesticide residues on medical marijuana plant material and marijuana products produced from marijuana cultivated by **Tree of Wellness INC, dba Tree of Wellness.** CDPHE and DOR deem it a threat to public health and safety when pesticides that are not on the list of approved pesticides for marijuana use as determined by CDA are applied in a manner inconsistent with the pesticide's label. CDA confirmed the presence of the Off-Label Pesticides, Myclobutanil, in the product samples tested.

Affected products include marijuana flower, trim, concentrates, and infused-products. Consumers who have these affected products in their possession should return them to the medical center from which they were purchased so they can be properly disposed of.

All affected marijuana has a label affixed to the container that at a minimum indicates the license number of the medical marijuana business that cultivated the marijuana. Consumers should check the label of their medical marijuana for the following license number and harvest batch numbers:

Medical Optional Premises Cultivation License 403-00664 and/or Medical Marijuana Center License 402-00443

Agent Orange 9.8.17	Chewbacca 10.17.17	Lemon Diesel 9.22.17
Blue Dream 10.16.17	Chewbacca 8.14.17	Lemon Diesel 9.8.17
Blue Dream 10.2.17	Chewbacca 9.8.17	Nightmare Cookies 7.19.17
Blue Dream 4.8.17	Critical Mass 7.1.17	Nightmare Cookies 9.8.17
Blue Dream 8.14.17	Critical Mass 9.1.17	Northern Lights 10.16.17
Blue Dream 9.1.17	Durban Poison 7.31.17	Northern Lights 10.2.17
Blue Dream 9.21.17	Durban Poison 8.14.17	Northern Lights 7.31.17
Blue Dream 9.8.17	Durban Poison 9.1.17	Northern Lights 8.14.17
Buddah Tahoe 7.1.17	Durban Poison 9.27.17	Northern Lights 9.1.17
Buddah Tahoe 8.14.17	Fluffhead 7.19.17	Pink Kush 7.19.17
Cali Orange 10.2.17	Fruity Pebbles 7.19.17	Pink Kush 8.14.17
Cali Orange 5.23.17	Fruity Pebbles 8.1.17	Pooty Tang 10.16.17
Cali Orange 8.1.17	ICE 9.8.17	Pooty Tang 9.1.17
Celemntine 10.17.17	Lemon Diesel 3.23.17	Pooty Tang 9.21.17

Pooty Tang 9.8.17
Purple Headband 10.2.17
Purple Headband 10.23.17
Purple Headband 9.1.17
Purple Headband 9.8.17
Purple Urkel 7.19.17
Purple Urkel 7.31.17
Purple Urkel 9.1.17
Purple VooDoo 7.31.17
Purple VooDoo 9.1.17
Purple VooDoo 9.21.17
Sour Kush 7.1.17
Sour Kush 9.1.17
White Bubba 10.16.17
White Bubba 7.31.17
White Bubba 9.22.17
White Bubba 9.8.17
XXX Diesel 10.16.17
XXX Diesel 10.2.17
XXX Diesel 8.14.17
XXX Diesel 9.8.17

ELMER PRESS

Case Report

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Disseminated Intravascular Coagulopathy Secondary to Unintentional Brodifacoum Poisoning via Synthetic Marijuana

Abigail Chan[a, c], Michael Adashek[a], Julian Kang[a], Adriana Medina[b]

Abstract

Recent evidence demonstrates a rising epidemic of unintentional brodifacoum poisoning associated with synthetic cannabinoid use. Synthetic cannabinoid use is on the rise because of its inexpensiveness as well as difficulty to screen and regulate. We present a rare case of severe coagulopathy and cardiac arrest secondary to synthetic cannabinoid use complicated by brodifacoum toxicity.

Keywords: Disseminated intravascular coagulopathy; Synthetic marijuana; Brodifacoum poisoning

Introduction

Synthetic cannabinoids (SCs) are inexpensive and have quickly spread worldwide since introduction in the early 21st century. The multiple analogs of SCs render urine drug testing difficult [1] and routine urine toxicology ineffective [2]. This subsequent explosion in SC use has coincided with an alarming increase in complications including myocardial infarction [2-6], cerebrovascular disease [7, 8], psychosis [9], seizures [10], acute kidney failure [11-14], and death [3, 15]. We present a rare case of severe coagulopathy and cardiac arrest secondary to SC and unintentional brodifacoum exposure.

Case Report

A 38-year-old man with previous diagnoses of bipolar disorder, post-traumatic stress disorder and polysubstance abuse presented with a 3-day history of epistaxis, hematuria, rectal bleeding, bruising and diffuse abdominal pain. His medical history was positive for daily marijuana as well as synthetic marijuana use and was otherwise negative. Vital signs were normal. His physical exam was significant for ecchymosis of the abdomen and extremities.

Initial workup was remarkable for elevated prothrombin time (PT) at > 154 s (normal range (NR): 9.2 - 11.8 s) and activated partial thromboplastin time (aPTT) at > 169 s (NR: 23 - 30 s), as well as an undetectably high international normalized ratio (INR) (NR: 0.9 - 1.1 s). D-dimer was reported to be > 35 mg/L (NR: 0.19 - 0.9 mg/L), lactate dehydrogenase (LDH) was elevated at 582 Unit/L (NR: 84 - 246 Unit/L) and low fibrinogen was 64 mg/dL (214 - 407 mg/dL) without schistocytes on peripheral blood smear. Liver function tests were within normal limits. His complete blood count showed white blood cell count (WBC) of 9,870/mm^3, hemoglobin of 15.9 g/dL, hematocrit of 47.2%, and platelets of 287,000/mm^3. Urine toxicology was positive for both cannabinoids and opioids, and urinalysis was consistent with hematuria.

The patient was diagnosed with disseminated intravascular coagulopathy (DIC). Initial resuscitative efforts included intravenous fluids, fresh frozen plasma, cryoprecipitate, vitamin K1, and factor IX concentrate. The patient was found hours later outside his hospital room unconscious and in pulseless electrical activity (PEA) arrest. The patient did have return of spontaneous circulation but the etiology of his cardiac arrest remained unknown. Maryland Poison Control was contacted, who were concerned for potential brodifacoum-laced synthetic cannabinoid use. Over the course of his hospital stay, he required immense doses of vitamin K1, in oral and intravenous doses. His INR trends and treatment measures are depicted in Figure 1.

The patient was successfully discharged on daily oral vitamin K with a discharge INR of 1.1. Unfortunately, the patient was noncompliant with his medication and presented 3 days after discharge to the emergency department with new onset left upper extremity deep vein thrombosis and an INR of 7.2. He was given intravenous vitamin K in the emergency department but left against medical advice and was lost to follow up.

Discussion

SC toxicity is on the rise in the United States of America

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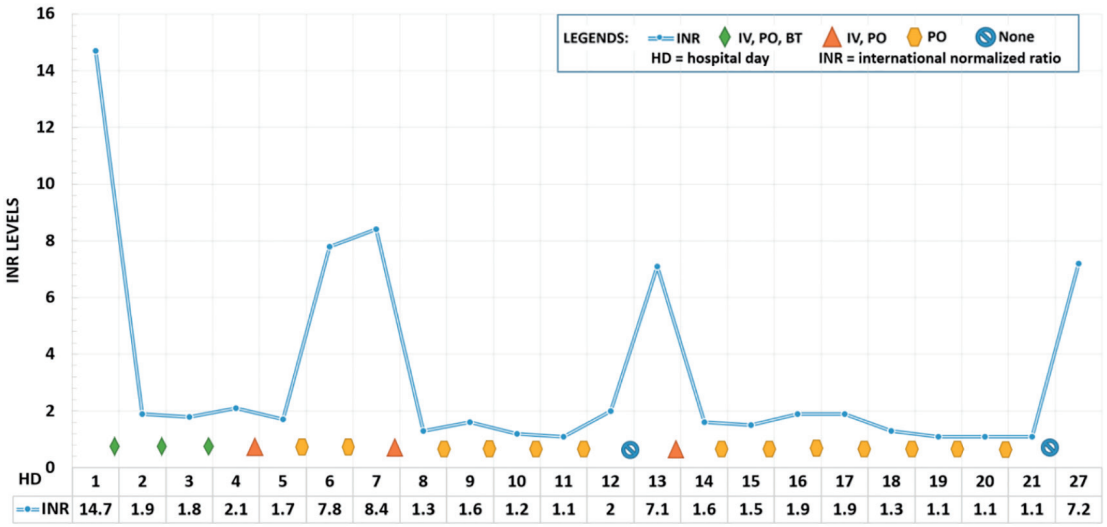

Figure 1. Daily INR level and treatment regimen while hospitalized. INR on admission was extrapolated from aPPT levels. Initial treatment utilized intravenous and oral vitamin K, reduced to oral vitamin K supplementation alone on day 5, with intermittent infusions. He refused the dose on day 12. Patient was discharged on day 21. He returned to the emergency room on day 27. BT: blood transfusion; IV: intravenous vitamin K1; PO: oral vitamin K1; HD: hospital day; INR: international normalized ratio.

(USA) [16]. SCs come in many varieties, and clinicians should be aware of the current monikers including "Spice", "K2", "Cloud 9" among many others [17]. Common symptoms of SC exposure consist of agitation, depression, psychosis and coma [16] as well as tachycardia, hypertension, chest pain, hallucinations and vertigo [17]. A recent case series demonstrated that out of 456 patients treated for SC intoxication, 277 reported SC as the sole toxic agent. Among these cases, >25% occurred in the pediatric population between ages 13 and 18 years old, and 83.1% of patients were male [16]. Caviness et al reported that SC use often coincides with binge drinking and recreational drug use including marijuana [18]. No antidotes to the effects of SCs currently exist [16].

From March to July of 2018, the Illinois Department of Health reported 255 patients with SC-associated coagulopathy, and eight mortalities [19]. Kelkar and colleagues identified 34 patients with SC-associated coagulopathy with a mean age of 37 years old, and presenting symptoms of gross hematuria and abdominal pain. Mean INR on presentation was 15.8. Vitamin K1 (phytonadione) was given orally to all patients and 68% of cases were supplemented with intravenous vitamin K1, 55% with fresh frozen plasma, and one case with 4-factor prothrombin complex concentrate. Eight patients left against medical advice and six were subsequently readmitted. Serum samples from these patients tested positive for brodifacoum [20]. As of January 1, 2019, the Maryland Poison Center at the University of Maryland School of Pharmacy reported notification of 44 cases with exposure to SC with significant elevations in INR and hemorrhage with 9% mortality [21].

In the USA, synthetic cannabis production remains illegal in federal law, and therefore federally unregulated [22]. At this time, it is unknown how brodifacoum was incorporated into the patient's SC; however, in cannabis production facilities, brodifacoum is often applied to the base of Cannabaceae stalks as a rodenticide. Quantities up to 25 kg can be found at these facilities, and have been correlated to an increased death toll on local animals [23]. Compared to warfarin, the strong hydrophobicity in brodifacoum allows for longer tissue retention, a half-life lasting from 20 days to 12 months, and a potency 100 times stronger than warfarin in reducing vitamin K-dependent coagulation factors [24]. Toxicity in rat models was higher when inhaled than ingested [25]. Unfortunately, diagnosis remains difficult. A recent study by Ng et al stated that in 41 identified cases of extended release warfarin toxicity, 25% of patients did not have obvious exposure history, nor could identify the causative agent. Occult poisoning was frequently missed on initial clinician visit, leading to delayed initiation of treatment [26].

The Saint Frances Medical Center in Illinois has developed a criterion to diagnose SC-associated coagulopathy. Major criteria include: 1) presence of vitamin K-dependent factor coagulopathy (defined as a prothrombin time $\geq$ 14.8 s and an INR $\geq$ 1.3); and 2) recent exposure to SCs (within the past 30 days). The minor criteria include: 1) active bleeding symptoms; 2) exposure to contaminated SCs obtained from a person with known superwarfarin poisoning; and 3) positive toxicology for superwarfarin. The use of prescribed anticoagulants was listed as a confounding factor. Patients with both major criteria and at least one minor criterion were diagnosed with SC-associated coagulopathy. In cases of concurrent anticoagulant use, an anticoagulant poisoning panel, which detects warfarin, dicumarol, diphacinone, chlorophacinone, difenacoum, brodifacoum, and bromadiolone, was utilized [20].

Treatment of brodifacoum toxicity depends greatly on the method of poisoning [27]. Studies in a canine animal model have demonstrated that if emesis is induced within 1 h of ingesting brodifacoum rodenticide, 10-77% of brodifacoum is expelled with the gastric contents. In this canine population, all the animals did well without further medical treatment and

did not require further medical intervention [28]; however, this has not been studied in a human model. In humans, the rapid correction of severe coagulopathy can be achieved with a combination of the following interventions: fresh frozen plasma, recombinant activated factor VII, prothrombin complex concentrate, intravenous and oral vitamin K1 [24].

In all cases of brodifacoum toxicity with elevated PT, vitamin K1 should be administered via slow intravenous injection of 10 - 25 mg every 3 - 6 h until PT has normalized. Subsequently the patient should be prescribed 10 mg of oral vitamin K1 four times a day [27]. Extensive follow-up and monitoring for months will be required due to brodifacoum's half-life with eventual taper of oral vitamin K1 [24, 27]. The financial burden on the patient and the healthcare system is a great one, as a 1-month supply of vitamin K1 costs between $24,000 and $34,000 (US dollars) [20].

In conclusion, there is evidence of a rising epidemic of brodifacoum poisoning as a result of SC use. There may be some evidence that brodifacoum is used as a rodenticide to maximize crop production from illegal synthetic cannabis producing facilities, and the toxicities are passed along to uninformed consumers. If acutely ingested, emesis is a viable initial option as front-line treatment, while results of PT and aPTT are pending. Supportive measures and treatment with vitamin K1 should be initiated once the coagulability is identified and continued on discharge. Long-term administration of vitamin K1, frequent laboratory monitoring, and close follow-up with medical providers comes at a high cost and an interdisciplinary team consisting of medical providers, pharmacists and social workers are warranted. Synthetic cannabis use in the pediatric population is especially concerning, and pediatricians as well should be vigilant for signs of hematuria, ecchymosis, abdominal pain or rectal bleeding as all may be an initial sign of brodifacoum toxicity. This is an impending public health crisis that many providers may face, and through both public awareness and health education can brodifacoum toxicity be addressed.

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Financial Disclosure

None of the authors have any financial or personal bias to declare.

Conflict of Interest

None.

Informed Consent

Manuscript has been anonymized and no identifiable information has been included in the manuscript.

Author Contributions

AC, MA, JK and AM equally contributed in the writing of the paper. All authors edited and approved the final manuscript.

Abbreviations

aPTT: activated partial thromboplastin time; BT: blood transfusion; DIC: disseminated intravascular coagulopathy; HD: hospital day; INR: international normalized ratio; IV: intravenous; LDH: lactate dehydrogenase; NR: normal range; PEA: pulseless electrical activity; PO: oral; PT: prothrombin time; SC: synthetic cannabinoid; WBC: white blood cell count; USA: United States of America

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