DRUG FREE AUSTRALIA

Cannabis no longer a medical option

1. New population studies in medical journals over the last 30 months have shown cannabis causes more cancers than tobacco - as well as a host of serious birth defects - given its proven genotoxic and mutagenic nature. Cannabis is now understood to be more toxic than tobacco, and therefore is no longer a reasonable option for widespread medical use
2. The harms of cannabis use outweigh any modest medical benefit
3. *De facto* legalised recreational use has been the result of lax medical cannabis laws in the US which later were the pathway to legalised recreational use. It is imperative WA not make this error given the newly understood dangers of the substance
4. The UK has placed major limitations on cannabis for chronic pain and advises it only as a last resort. Despite the science, 61% of cannabis prescriptions here are for chronic pain
5. Current costs of using medical cannabis are similar to costs when it was illegally obtained
6. Cannabis clinics in Sydney, when called, stated that in their view there are no major impediments to obtaining medical cannabis in this country

Central Issues
&
Compiled Evidence

The situation for cannabis has changed.

In the last few years the already demonstrated genotoxic and mutagenic nature of cannabis has been confirmed at the population level – it has been found to cause five more cancers than tobacco and is causal in 2/3rds of the 62 birth defects tracked by the US Centre of Disease Control (CDC).

In the view of Drug Free Australia, this Inquiry needs to put aside all mooted plans for liberalising cannabis laws and rather shift its efforts into alerting Western Australians of the now better-understood harms of cannabis, whether used medicinally or recreationally.

DRUG FREE AUSTRALIA

Six Central Issues for the WA Cannabis Inquiry

1. **Western Australian legislators must now reckon with medical journal studies demonstrating that cannabis, including Cannabidiol (CBD), causes more cancers than tobacco, as well as many birth defects caused by alterations to both the father's and mother's chromosomes by cannabis' genotoxic and teratological mechanisms**

   Tobacco is not considered a medical option because its harms, particularly the many cancers it causes, outweigh its few benefits. The same is true of cannabis, where new population studies have now shown that its previously well-known genotoxic and teratological properties are demonstrably damaging whole populations of cannabis users as well as future generations of Australians where cannabis-caused dangerous mutations will be inherited by 3-4 generations of children and grandchildren of cannabis users. Cannabis should now only be used for very serious conditions where there is absolutely no alternative

2. **The harms of cannabis use outweigh any modest medical benefit**

   Beyond cancers and birth defects, Cannabis is an addictive drug which causes psychosis, depression, suicide, violence, vehicle deaths, amotivational syndrome, immunosuppression, permanent harms to the unborn as well as cardio and pulmonary conditions

   Any medical benefit from the use of medical cannabis for any Australian individual must outweigh these harms, particularly when pot activists are agitating for a loosening of very reasonable and equitable regulatory requirements which are identical for all medicines within Australia. The deficits for cannabis are now known to be so great it is no longer viable for general medical use, let alone recreational use

3. **To illustrate how State laws can cause more harm than good, *de facto* legalised recreational use of cannabis has been the result of lax medical cannabis laws in the US – Australia must avoid doing the same. The same lax medical cannabis laws**

were the pathway to legalised recreational use in the US, so it is again imperative that Australian States not make this mistake

The US has witnessed a medical cannabis rort where recreational users feign unverifiable chronic pain maladies to access high quality cannabis availability. This ruse effectively 'legalises' the constant use of cannabis for what is, in reality, only recreational use. Western Australia must avoid bowing to pressure groups wishing to establish such a pathway

In light of 80% of Australians not approving of recreational cannabis use, the legalisation of cannabis for recreational use in Colorado and other US States gives voluminous evidence on why the WA Government must ensure that medical cannabis, for those few conditions that remain viable, is not used as a pathway to legalised recreational use in this country

To illustrate why recreational cannabis should never be legalised, Colorado and Washington were the first states to legalise recreational use, having previously legalised medical cannabis. Within a year of legalisation in 2014 cannabis use by those aged 12-17 had risen 20% against decreases of 4% for all other states, rising 17% for college age young people against 2% for other states – all despite cannabis being illegal for all under age 21. Most notably, adult use rose 63% against 21% nationally

According to the US SAMHSA household survey, those reporting they had used cannabis in the last month before survey increased by a staggering 245,000 between 2010 (when medical cannabis was commercialised) and 2015. This 43% increase in frequent cannabis use creates a vast new population susceptible to the multitude of harms presented by cannabis

When comparing three-year averages before and after legalisation, cannabis-related traffic deaths rose 62%. Hospitalisations related to cannabis went from 6,715 in 2012 to 11,439 in 2014. Notably, black market criminals found new sanctuary in Colorado, attracted by lower risks of enforcement. Governor Hickenlooper introduced House Bill 1221 to address the 380% rise in arrests for black market grows between 2014 and 2016

Colorado's experience is a cautionary tale of what Australia must necessarily avoid. Ineffective medical cannabis laws will only promote what Australians clearly do not want

4. **The UK recognises the limitations of cannabis on chronic pain and advises it only as a last resort yet 61% of Australians use it,**

despite demonstrated lack of effectiveness, for 'chronic pain'

5. **Current costs of using medical cannabis are directly comparable to costs when it was illegally obtained**

6. **Cannabis clinics in Sydney, when called, stated that in their view there are no major impediments to obtaining medical cannabis**

The evidence supporting each of the six central issues nominated here is found in the following pages.

RECOMMENDATIONS

1. **That the WA Cannabis Inquiry make a priority of informing Western Australians of the very significant dangers of cannabis and synthetic cannabinoids, given the now-well-demonstrated genotoxic and mutagenic nature of cannabis,**
    - **that it causes 5 more cancers than tobacco;**
    - **that this includes Cannabidiol (CBD) which is wrongly perceived to be benign**
    - **that it causes numerous birth defects**
    - **that these cannabis-caused and dangerous mutations are likely to be inherited by the children and grandchildren of cannabis users**
    - **that this damage is done whether used medically or recreationally**

2. **That the WA Inquiry explore the legal exposures for State Parliamentarians who knowingly move to liberalise laws, broadening use of a toxic and damaging substance which causes more damage than tobacco, given that liberalisation of laws regarding cannabis use – both medically and recreationally – leads to significant increases in the uptake and use of the substance,**

3. **That the WA Inquiry press the Federal Government to not loosen any requirement for medical cannabis to meet the same TGA standards as any other medicine within Australia, where efforts to relativise TGA guidelines are in many cases intentioned attempts to provide a pathway to recreational use under the guise of medical use, given that there are very few medical conditions for which cannabis is used that don't have better medical alternatives**

4. **That the WA Inquiry review the UK approach to chronic pain with a view to suggesting similar better approaches in Australia**

5. **That the WA Inquiry examine the number of approvals of medical cannabis for chronic pain in Western Australia, and in light of chronic pain being used as a wide-spread ruse to create *de facto* legalised cannabis use, to recommend a media campaign to highlight alternatives and to air the issue for Western Australian medical cannabis users and their doctors**

6. **That the WA Inquiry prioritise funding for drug rehabilitation centres to ensure as many Western Australians as possible are given the opportunity to cease cannabis use for the sake of their individual and future generations' health**

7. **That the WA Inquiry survey the street costs of purchasing illicit raw cannabis leaf/bud and compare this to the costs of pharmaceutical preparations of medical cannabis – where our analysis demonstrates that they are the same, especially for those very few medical conditions such as childhood epilepsies for which there is no medicinal alternative to cannabis**

Table of Contents

CENTRAL ISSUES FOR THE WA CANNABIS INQUIRY – 1

Western Australian legislators must now reckon with medical journal studies demonstrating that cannabis, including Cannabidiol (CBD), causes more cancers than tobacco, as well as many birth defects caused by alterations to both the father's and mother's chromosomes by cannabis' genotoxic and teratological mechanisms

Tobacco is not considered a medical option because its harms, particularly the many cancers it causes, outweigh its few benefits. The same is true of cannabis, where new population studies have now shown that its previously well-known genotoxic and teratological properties are demonstrably damaging whole populations of cannabis users as well as future generations of Australians where cannabis-caused dangerous mutations will be inherited by 3-4 generations of children and grandchildren of cannabis users. Cannabis should now only be used for very serious conditions where there is absolutely no alternative

Science journal 'Nature' (July 2021) on genotoxic nature of cannabis

One of the world's two most respected scientific journals published a study https://www.nature.com/articles/s41598-021-93411-5 of cannabis use in the United States as it relates to Center of Disease Control (CDC) tracking of cancers and birth defects in that country.

Because there are varying legislative cannabis regimes – cannabis legalised for recreational use, cannabis legalised for medical use, decriminalised cannabis for recreational use, cannabis illegal for any use – which are distinct within the 50 States, the United States allows solid State by State comparisons where average cannabis use, as surveyed in each State via national survey instruments, can be compared with State disease and birth defect prevalence against those surveyed rates of cannabis use. DEA seizures of cannabis in each State, and their publication of cannabinoid strengths in tested cannabis can likewise add more specificity to these comparisons. Confounders are also excluded, as is required of any ecological study. With longitudinal data thus mapped in a spatial-temporal manner, the likelihood of cannabis being causal can also be judged.

The Nature study scrutinises data from 2003-2017 against five cancers and five birth defects to illustrate the spatio-temporal conclusions that can be drawn from the data. It is this same methodology that has driven conclusions which now demonstrate that cannabis is more toxic than tobacco, particularly as it relates to the causation of cancers and birth defects.

Cannabis' mechanism for causing mutations well described

In 2016 the mechanisms for cannabis' action on chromosomes, thus causing the mutations which drive cancer and birth defect increases, were drawn together in the medical journal Mutation Research, drawing together decades of previous research on the effects of cannabis at the molecular biology level.

Mutation Research 789 (2016) 1–11

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity

Albert Stuart Reece*, Gary Kenneth Hulse

School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA 6009, Australia

ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form 17 April 2016
Accepted 1 May 2016
Available online 4 May 2016

Keywords:
Cannabis
Microtubules
Tubulin
Dose-response relationship
Threshold dose
Population effects
Oncogenesis
Foetal malformations
Chromothripsis
Epigenetics
Transgenerational
Heritable
Interdisciplinary

ABSTRACT

The recent demonstration that massive scale chromosomal shattering or pulverization can occur abruptly due to errors induced by interference with the microtubule machinery of the mitotic spindle followed by haphazard chromosomal annealing, together with sophisticated insights from epigenetics, provide profound mechanistic insights into some of the most perplexing classical observations of addiction medicine, including cancerogenesis, the younger and aggressive onset of addiction-related carcinogenesis, the heritability of addictive neurocircuitry and cancers, and foetal malformations. Tetrahydrocannabinol (THC) and other addictive agents have been shown to inhibit tubulin polymerization which perturbs the formation and function of the microtubules of the mitotic spindle. This disruption of the mitotic machinery perturbs proper chromosomal segregation during anaphase and causes micronucleus formation which is the primary locus and cause of the chromosomal pulverization of chromothripsis and downstream genotoxic events including oncogene induction and tumour suppressor silencing. Moreover the complementation of multiple positive cannabis-cancer epidemiological studies, and replicated dose-response relationships with established mechanisms fulfils causal criteria. This information is also consistent with data showing acceleration of the aging process by drugs of addiction including alcohol, tobacco, cannabis, stimulants and opioids. THC shows a non-linear sigmoidal dose-response relationship in multiple pertinent *in vitro* and preclinical genotoxicity assays, and in this respect is similar to the serious major human mutagen thalidomide. Rising community exposure, tissue storage of cannabinoids, and increasingly potent phytocannabinoid sources, suggests that the threshold mutagenic dose for cancerogenesis will increasingly be crossed beyond the developing world, and raise transgenerational transmission of teratogenicity as an increasing concern.

The key observation is that cannabis pulverises or shatters particular chromosomes and, in the process of chromothripsis, the DNA repair mechanisms may not correctly do their work, causing mutations which are causal in both cancers and birth defects. This pulverisation can be seen in one of the graphics reproduced in that study.

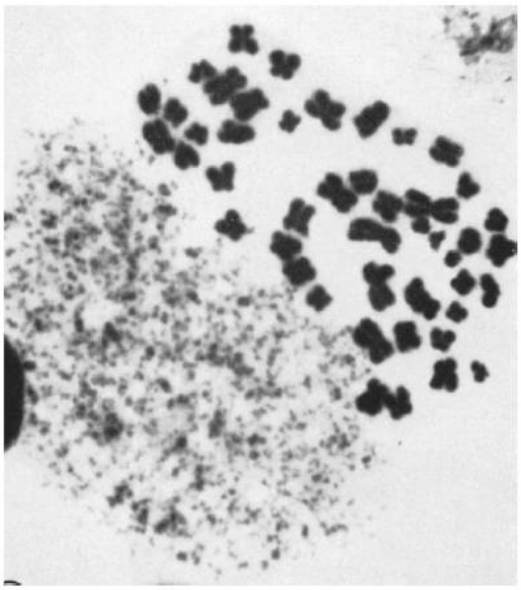


Fig. 1. Chromosomal Pulverization.
Original Report of Chromosomal Pulverization. Figure 7 , Kato H., Sandberg AA (1967). "Chromosome Pulverization in Human Binucleate Cells. Following Colcemid Treatment." J. Cell Biol. 34 (1): 35–45. Re-used by permission.

This has led to the more detailed population studies of the relationship between cannabis, cancer and birth defects which have been published in the last two years.

Cannabis causal in rising pediatric cancers (February 2021)

The February 2021 study in the medical journal BMC Cancer https://pubmed.ncbi.nlm.nih.gov/33632159/ 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 should most certainly never 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*.

The recent study by Professors Stuart Reece and Gary Hulse from the University of Western Australia uses sophisticated geospatiotemporal modelling to study correlations between the rising cancer rates and cannabis use in US States with 4 different illegality/legality regimes - those where it remains illegal versus those states that have decriminalised cannabis versus legalised it for medical and for

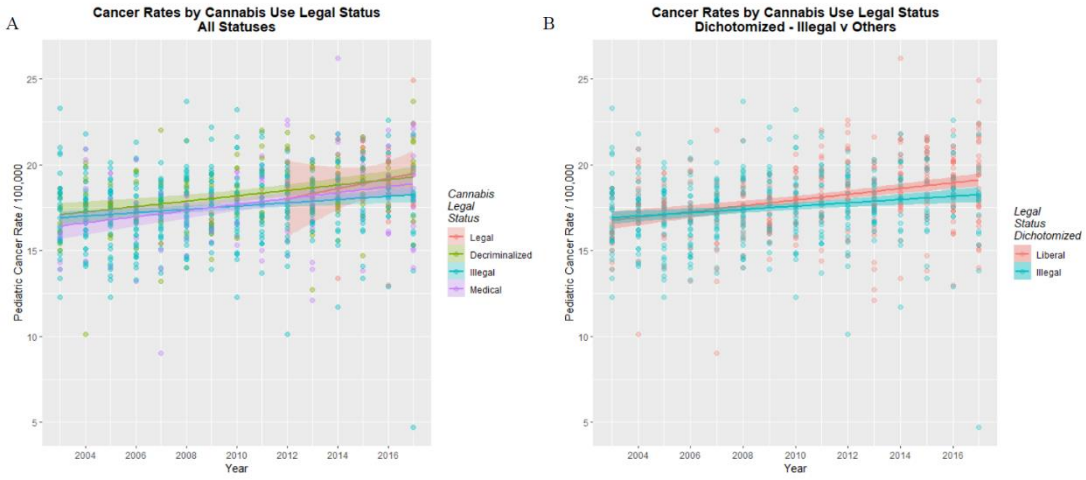
recreational use. Cannabis use for each US State, using data from the National Survey of Drug Use and Health (NSDUH), was tracked along with use of tobacco, alcohol, cannabis, opioid analgesics and cocaine for comparison. The use of all drugs have been falling nationally in contrast to increases in cannabis use over the comparison period of 2003-2017. All data was checked against cannabis use according to ethnicity as well as household income.

Cannabis legalisation was associated with higher rates of pediatric cancer, as were States where cannabis has been made legal for medical purposes or has been decriminalised. Drug seizure data across all years of the study period from the US Drug Enforcement Agency indicate that rising levels of THC and the cannabinoid Cannabigerol are more specifically correlated to the rising levels of these cancers. Causality was demonstrated via the intersection of statistical associations over space and time, along with additional methods for ensuring no other unforeseen causal factors.

The study also dealt with known biological mechanisms by which cannabis might cause pediatric cancers. There is already a substantial science addressing these mechanisms, demonstrating that cannabis does lasting damage to DNA in a variety of ways. This genetic damage affects both the mother and father of a child, with childhood cancers possibly attributed to both.

Increases in 7 major pediatric cancers, which comprise up to 70% of all pediatric cancers, were correlated with rising cannabis use in various US States but with further attention paid to causality rather than mere correlation. The link between cannabis and pediatric cancers relied on previous studies:

Below is the relationship between the legal status of cannabis in varying US States which drives the increased use of cannabis according to the varying legal or decriminalised drug policy regimes. The result of this study is that cannabis is causal in the 49% rise in a majority of pediatric cancers in the US, with a clear causal mechanism having already been explicated.



Cannabis causal in rising rates of birth defects (July 2019)

In July 2019 cannabis was shown to be causal, at the population level, in rising rates of birth defects, with the following study in Clinical Pediatrics https://journals.sagepub.com/doi/full/10.1177/0009922819861281.

As per the studies abstract:

> Rising Δ9-tetrahydrocannabinol concentrations in modern cannabis invites investigation of the teratological implications of prenatal cannabis exposure. Data from Colorado Responds to Children with Special Needs (CRCSN), National Survey of Drug Use and Health, and Drug Enforcement Agency was analyzed. Seven, 40, and 2 defects were rising, flat, and falling, respectively, and 10/12 summary indices rose. Atrial septal defect, spina bifida, microcephalus, Down's syndrome, ventricular septal defect, and patent ductus arteriosus rose, and along with central nervous system, cardiovascular, genitourinary, respiratory, chromosomal, and musculoskeletal defects rose 5 to 37 times faster than the birth rate (3.3%) to generate an excess of 11 753 (22%) major anomalies. Cannabis was the only drug whose use grew from 2000 to 2014 while pain relievers, cocaine, alcohol, and tobacco did not. The correlation of cannabis use with major defects in 2014 (2019 dataset) was $R = .77$, $P = .0011$. Multiple cannabinoids were linked with summary measures of congenital anomalies and were robust to multivariate adjustment.

Again it is cannabis use by both the father and the mother, and not just during pregnancy, which is driving these increases in birth defects.

As Western Australian parliamentarians consider any changes to WA law concerning the use of cannabis, such population studies which confirm decades of previous research into the physiological impacts of cannabis must now determine whether cannabis is suitable for medical use excepting those very serious conditions for which there are no alternatives.

Cannabis causal in at least 38 out of 62 recorded birth defects (March 2021)

In a backgrounder to a media release on the BMC Cancer study on pediatric cancers, communication from the lead author of the study gave information on the latest studies being sent to medical journals for publication.

This communication from Dr Stuart Reece, University of Western Australia, with Drug Free Australia was added as a media Backgrounder and stated the following:

> Cannabis genotoxicity is not controversial. It has been known since the 1960's, and many currently available cannabinoid products carry the standard genotoxic warnings on them against their use in pregnancy and lactation.

Cannabis genotoxicity has been well described from detailed molecular, cellular and lab animal test from the 1960's with serious birth defects described. We have been reviewing national epidemiological patterns around the world and confirmed a much higher rate of total birth defect in the north of Canada which smokes more cannabis; in the northern rivers area of NSW and in Colorado following cannabis legalization. We just showed that a common defect is also contributed to by cannabis, babies born with holes in their heart. Others published similar findings on Hawaii in 2007.

We are presently reviewing the total US cancer database 2001-2017. Dozens of cancers are related epidemiologically and causally to cannabis consumption. As you are aware I am presently writing up a major resource document on cannabis genotoxicity and we are given to understand that it is likely to be published by one of the United Nations bodies concerned with this area.

Many cannabinoids are implicated including particularly cannabidiol.

Cannabis and cannabinoids are more potent carcinogens and teratogens than tobacco or alcohol.

This situation recapitulates precisely what was done in 1957 when a known genotoxin was marketed for commercial gain, actually for indications of nausea, morning sickness, tiredness depression and fatigue, just as cannabis, cannabis oil and cannabidiol are today.

Of course the objections to cannabis are not limited to genotoxicity. In a general order of relative concern:

1) Neurotoxicity
    i) Adverse effects on many mental illnesses
    ii) High incidence of autism spectrum disorders in children exposed in utero
    iii) "Stoner" anhedonia lethargy, unemployment / unemployment / long term unemployment / welfare dependency consequent upon reduced achievement of major life goals – jobs, relationships, personal stability
    iv) Driving is adversely affected. Moreover alcohol is legal and the combination of alcohol and cannabis adversely affects road safety in a multiplicative fashion
    v) Cannabis was shown to be a gateway drug to other drug use in New Zealand, Australia and USA 20 years ago.
    vi) Damage to the cerebellum and frontal lobes shown on PET Scan neuroimaging causing problems in motor skills, coordination, memory and learning.
2) Genotoxicity
    i) Cancer development – 14-24 / 34 cancers are implicated in with increased cannabis use in USA on geospatial and odds ratio criteria respectively.
    ii) 38-44 of the 62 birth defects tracked by CDC National Birth Defect Prevention Network are increased in high cannabis using areas of USA.

iii) Strongly linked with testicular cancer in all four studies on this issue.
iv) Direct damage to chromosomes which carry the genes and causes cancer and birth defects
v) Direct damage to genes and chromosomes some of which can be passed to subsequent generations and is known to cause cancer and birth defects
vi) Damage to the “epigenome” which is the cellular software which controls the genes and is known to be inherited at least for generations and has been linked with cancer, birth defects and ageing
vii) Cannabis smoke has all the tars and carcinogenic toxins as cigarette smoke in addition to all the unique cannabinoids, many of which are themselves carcinogenic

3) Respiratory illness of many kinds is common with heavy cannabis use – chronic bronchitis, emphysema, lung cysts, airway inflammation and pre-neoplastic changes
4) Adverse effect on immune system – both immunosuppression and immunodepression which accelerate aging and age-related degeneration of many tissues
5) Adversely affects reproductive function in both males and females; adverse effects on sperm and oocytes
6) Increased incidence of liver cirrhosis
7) Also causes heart attacks and strokes from cardiovascular damage
8) Adverse effects on bone metabolism – osteoporosis.

Professor Dr Stuart Reece,
University of Western Australia,
Edith Cowan University.

Cannabis causal in more cancers than tobacco

In the same communication from the lead author of the BMC Cancer study on cannabis and pediatric cancers, Dr Reece referenced their current work using the same spatio-temporal modelling to assess the causality of cannabis in regards to all cancers tracked by the US Centre of Disease Control.

> We are presently reviewing the total US cancer database 2001-2017. **Dozens of cancers are related epidemiologically and causally to cannabis consumption**. As you are aware I am presently writing up a major resource document on cannabis genotoxicity and we are given to understand that it is likely to be published by one of the United Nations bodies concerned with this area.
>
> Cannabis and cannabinoids are more potent carcinogens and teratogens than tobacco or alcohol.

i) **Cancer development – 14-24 / 34 cancers are implicated in with increased cannabis use in USA on geospatial and odds ratio criteria respectively.**

Even Cannabidiol (CBD) causes as many cancers as tobacco

It is notable that in the aforementioned communication by the lead author of the BMC Cancer study on pediatric cancers that Cannabidiol, which is currently being marketed as a safe and effective medicinal cannabinoid and wonder drug derived from hemp, is just as implicated as THC in causing adult cancers.

> We are presently reviewing the total US cancer database 2001-2017. Dozens of cancers are related epidemiologically and causally to cannabis consumption. As you are aware I am presently writing up a major resource document on cannabis genotoxicity and we are given to understand that it is likely to be published by one of the United Nations bodies concerned with this area.
>
> **Many cannabinoids are implicated including particularly cannabidiol.**

The same point is made in a radio interview with the Western Australian radio station Mix 94.5 where Pete, Matt and Kymba interview lead author Dr Stuart Reece from WA University.
https://www.righttobreathecannabisfreeoregon.org/post/cancer-causing-and-genotoxic-effects-of-cannabis-and-cbd

Cannabis-caused mutations inherited by 3-4 generations of progeny

From a 2016 journal study in Mutation Research https://pubmed.ncbi.nlm.nih.gov/27208973/ studying cannabis' causal mutation mechanisms regarding cancer and birth defect-causing, the researchers cite strong evidence that these mutations are passed to three and even four generations of cannabis users' progeny, multiplying the cancer and birth defect damage to the lives of the born and unborn for at least a century. They record:

> It will also be noted that the discussion to this point has not considered the epigenetic revolution which is rapidly overtaking medicine. The origins of the Barker hypothesis of the foetal origins of adult disease has been attributed to the observation of the increased incidence of cardiovascular disease in children born to women exposed to the post-war famine in England [138,139]. Since that time many environmental agents have been linked with epigenetic change including alcohol [140–142], cocaine [143–148], amphetamine [149–152], opioids [153–156] and cannabinoids [41,59,157,158]. Indeed epigenomic changes

have also been described with behavioural addictions such as gambling [159], and with stress exposure [160–164] which is a major

common factor shared amongst all addictive syndromes. Whilst some epigenetic changes have been shown to be reversible in the short term [163], **others have been shown to be passed on to offspring for three to four subsequent generations [165–167] via epigenetic modifications in oocytes and sperm [153,167–169].** Transgenerational transmission of epigenetic change through altered sperm DNA methylation has also been shown for cannabinoids in rats [157,170,171] and humans [172–174]. The well known immunmodulatory actions of cannabinoids also impact brain structure at sensitive developmental stages [62,175,176] and may be transferred to offspring epigenetically [62]. Since cannabinoids have long been known to selectively suppress nuclear histone mRNA and protein expression [43,50,177,178], alter the RNA transcriptome [157,171,179] and modify DNA methylation in key brain reward areas [157,170] thereby modifying all the main epigenomic regulatory systems, it seems inevitable that we are on the threshold of an exciting time to learn more about heritable pathways to genotoxic disease. Epigenetic inheritance has also been linked with paediatric gliomagensis [180]. Normal developmental [181] and ageing changes [182,183], cellular lineage specification amongst different tissues [181], single cell memory formation [62,183–185] and complex disease origins have been attributed in large part to epigenetic changes [186].

Implications for medical cannabis

The genotoxicity of cannabis has been known for decades, but it has taken the recent population studies of US CDC data on cancers and birth defects to demonstrate the impacts of cannabis at the population level. Cannabis is causal in two-thirds of the birth defects tracked by the CDC, and is causal for more cancers than tobacco. A study of European cancer data (in press) shows that cannabis causes 21 cancers (Europe tracks more cancers than in the US) as compared to tobacco's 16. Synthetic cannabinoids are not an alternative.

No doctor would prescribe tobacco, with its known harms. The same will be true of cannabis.

Drug Free Australia urges the Western Australian Parliamentary Inquiry to seek advice on legal liability accruing to Parliamentarians if laws on a toxic substance are knowingly loosened.

CENTRAL ISSUES FOR THE WA CANNABIS INQUIRY – 2

The harms of cannabis use outweigh any modest medical benefit

Beyond cancers and birth defects, Cannabis is an addictive drug which causes psychosis, depression, suicide, violence, vehicle deaths, amotivational syndrome, immunosuppression, permanent harms to the unborn as well as cardio and pulmonary conditions

Any medical benefit from the use of medical cannabis for any Australian individual must outweigh these harms, particularly when pot activists are agitating for a loosening of very reasonable and equitable regulatory requirements which are identical for all medicines within Australia. The deficits for cannabis are now known to be so great it is no longer viable for general medical use, let alone recreational use

World's most authoritative review indicates many harms but mostly only modest medical effectiveness

The world's most extensive 2017 review of cannabis journal studies by the US National Institutes of Health (NIH - previously the Institute of Medicine [IOM]) indicates that there are many harms accruing from the use of cannabis, while there are a handful of evidenced uses for medical conditions.

It is the harms of cannabis that make government regulation of cannabis necessarily rigorous. These harms include:

- 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 use is associated with a doubling the chance of psychosis
- Cannabis use is associated with a greater risk of depression
- Cannabis is associated with Amotivational Syndrome
- Cannabis use is associated with a 3-fold risk of suicidal ideation
- VIOLENCE AND AGGRESSION are a documented part of its withdrawal syndrome

- 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
- The already-covered causality of multiple cancers and birth defects
- Cannabis is also associated with cardio-vascular stroke and heart attack, with chance of myocardial infarction 5 times higher after one joint

On the other hand, cannabis has been shown to alleviate the following conditions, however for anything other than epilepsy-like syndromes, the effects are modest, where up to a dozen other available medications are often preferred by patients above medical cannabis.

As per the summary from the 468 page NIH review below, these conditions are:

1. **Chronic pain – modest effect only**
2. **Nausea**
3. **Multiple Sclerosis (MS) – modest effect only**
4. **AIDS wasting**
5. **Tourette Syndrome**
6. **Post Traumatic Stress Disorder (PTSD)**
7. **Traumatic brain injury, intracranial haemorrhage**
8. **Childhood Epilepsy (**these latter conditions were confirmed in US Epidiolex trials which were completed after the 2017 NIH review)

New medical indications must be part of a trial

The medical cannabis landscape has now changed with new population studies clearly showing that cannabis is causing more cancers than tobacco as well as 40-odd birth defects, including the accelerating numbers of autism. The newly demonstrated risks of cannabis use now limit reasonable medical cannabis use to a very small number of conditions where no alternative exists, such as childhood epilepsies (we will deal with the ineffectiveness of cannabis on chronic pain further on). Depending on the severity of these epilepsies, the alleviation of symptoms will still need to be weighed against the risks of cancer, as well as future generations affected with cancers and birth defects as a result of medical cannabis as an intervention.

Drug Free Australia has historically supported the viability of medical cannabis in Australia on the proviso that any newly identified medical indications for cannabis

are studied as part of a clinical trial or a closely-monitored and reported individual case.

It is imperative that this be the case, with many claims for cannabis previously evaporating in the trial setting.

As with any other medicine in Australia, cannabis preparations must be subjected to the same rigour and be pharmaceutically standardised in terms of dose, strength and purity. Anything less is to make exceptions for an addictive and otherwise dangerous substance.

Cannabis preparations must continue to be subject to the strictures the TGA applies to any other medicine in this country.

Following pages – facsimiles of the Annex to the US National Institutes of Health 2017 review on all cannabis studies to that date. We note that the US Institutes of Health review panel had prominent pro-pot researchers involved.

ANNEX

Report Conclusions[5]

Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids

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

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

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

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)

- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 *Conclusions—Cancer*

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

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

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

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/ acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 *Conclusions—Cardiometabolic Risk*

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

Chapter 7 *Conclusions—Respiratory Disease*

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

Chapter 8 Conclusions—Immunity

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

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

- The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use) (8-3)

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

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

Chapter 9 Conclusions—Injury and Death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress,

among pediatric populations in U.S. states where cannabis is legal (9-4b)

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

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, nonmedical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

Chapter 12 Conclusions—Mental Health

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

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

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

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

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- 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)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors

for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)
- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

Chapter 14 Conclusions—Cannaabis Use and the Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis Research

There are several challenges and barriers in conducting cannabis and cannabinoid research, including

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short-

and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

---

[1] As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

[2] See https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana (accessed January 5, 2017).

[3] *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

[4] Agencies may include the CDC, relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

[5] Numbers in parentheses correspond to chapter conclusion numbers.

CENTRAL ISSUES FOR THE WA CANNABIS INQUIRY – 3

To illustrate how State laws can cause more harm than good, *de facto* legalised recreational use of cannabis has been the result of lax medical cannabis laws in the US – Australia must avoid doing the same. The same lax medical cannabis laws were the pathway to legalised recreational use in the US, so it is again imperative that Australian States not make this mistake

The US has witnessed a medical cannabis rort where recreational users feign unverifiable chronic pain maladies to access high quality cannabis availability. This ruse effectively 'legalises' the constant use of cannabis for what is, in reality, only recreational use. Western Australia must avoid bowing to pressure groups wishing to establish such a pathway

In light of 80% of Australians not approving of recreational cannabis use, the legalisation of cannabis for recreational use in Colorado and other US States gives voluminous evidence on why the WA Government must ensure that medical cannabis, for those few conditions that remain viable, is not used as a pathway to legalised recreational use in this country

To illustrate why recreational cannabis should never be legalised, Colorado and Washington were the first states to legalise recreational use, having previously legalised medical cannabis. Within a year of legalisation in 2014 cannabis use by those aged 12-17 had risen 20% against decreases of 4% for all other states, rising 17% for college age young people against 2% for other states – all despite cannabis being illegal for all under age 21. Most notably, adult use rose 63% against 21% nationally

According to the US SAMHSA household survey, those reporting they had used cannabis in the last month before survey increased by a staggering 245,000 between 2010 (when medical cannabis was commercialised) and 2015. This 43% increase in frequent cannabis use creates a vast new population susceptible to the multitude of harms presented by cannabis

When comparing three-year averages before and after legalisation, cannabis-related traffic deaths rose 62%. Hospitalisations related to cannabis went from 6,715 in 2012 to 11,439 in 2014. Notably, black market criminals found new sanctuary in Colorado, attracted by lower risks of enforcement. Governor Hickenlooper introduced House Bill 1221 to address the 380% rise in arrests for black market grows between 2014 and 2016

Colorado's experience is a cautionary tale of what Australia must necessarily avoid. Ineffective medical cannabis laws will only promote what Australians clearly do not want

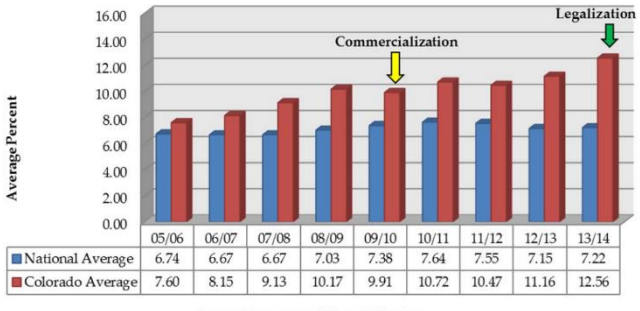
The results of cannabis legalisation is what Australians do not want

If there is any measure of what loose medical cannabis regimes lead to, Colorado and Washington in the US give the clearest picture. In 2013, Colorado and Washington introduced fully legalised recreational use of cannabis, with cannabis use by teens and college-age young people quickly increasing. Adult use doubled within three years, as detailed below. Likewise, various measures of harm also quickly increased.

Use of cannabis by those aged 12-17 rose 20% in first year

The legalisation of recreational use of cannabis in Colorado and Washington in 2014 has led to increasing drug use in those states. It is illegal for any under the age of 21 to use cannabis, especially given the effect of cannabis on the developing adolescent brain. But use in Colorado by those aged 12-17 rose substantially against decreases of 4% in other states, despite use already being elevated by the legalisation of medical cannabis.

Past Month Marijuana Use
Youth Ages 12 to 17 Years Old

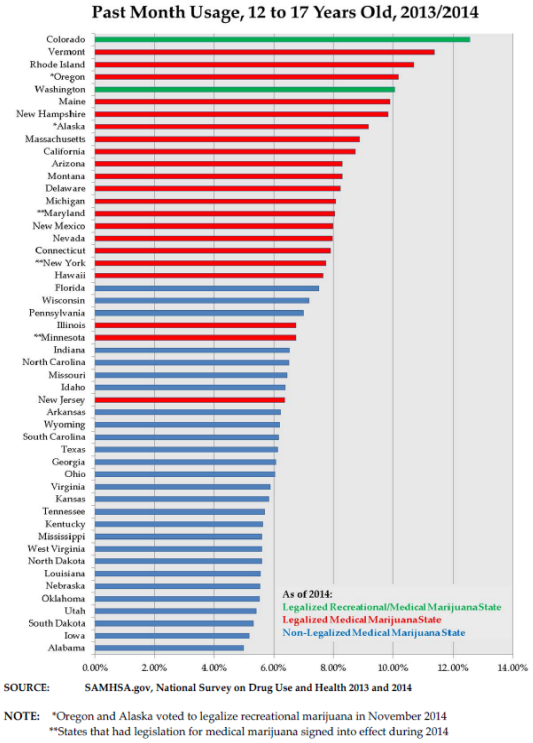


	05/06	06/07	07/08	08/09	09/10	10/11	11/12	12/13	13/14
National Average	6.74	6.67	6.67	7.03	7.38	7.64	7.55	7.15	7.22
Colorado Average	7.60	8.15	9.13	10.17	9.91	10.72	10.47	11.16	12.56

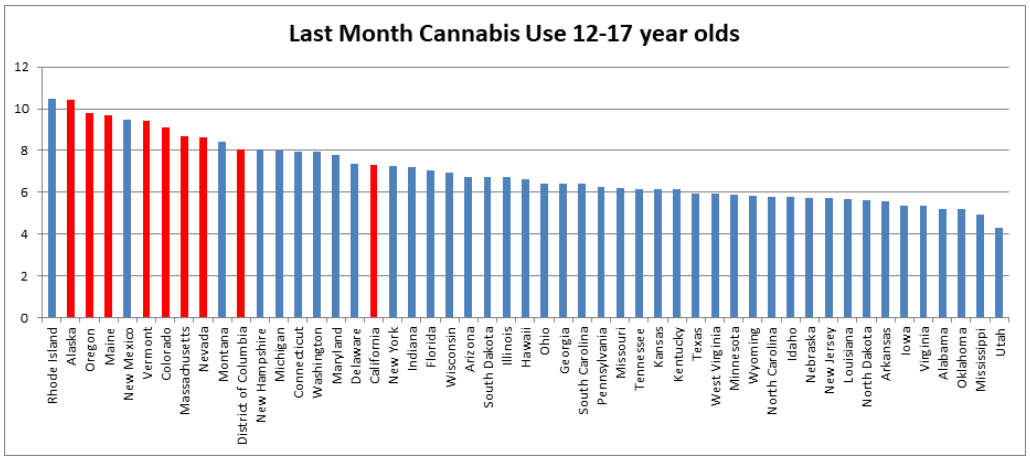
Annual Averages of Data Collection

SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014

In 2013/14 Colorado youth ranked #1 for cannabis use in the United States, up from #4 in 2011/12 and from #14 in 2005/6. In the graph below states with legalised medical cannabis are marked red, and green for recreational use.



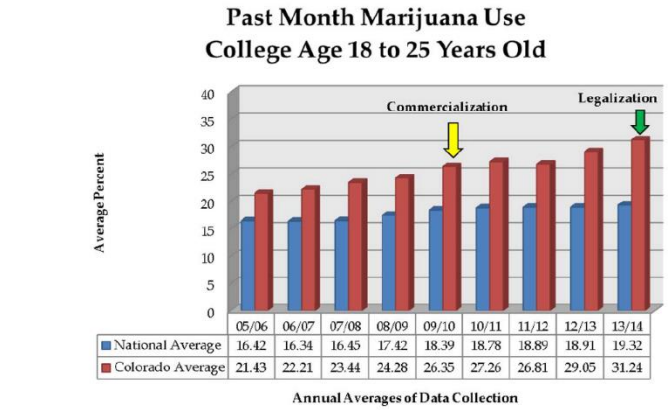
In the following 2 year period, drug use fell such that Colorado recent use for this age group fell to 7th in the nation. This was because other states had legalised cannabis in the intervening years, and Colorado was passed by states most of which had legalised cannabis use or were in the process of doing so. Below is the graph for all states with those states that had legalised cannabis by 2016 in red, or where legalisation legislation was already in process.



The most likely explanation for the marked decreases for this age-group is that they are under the institutional control of schools, whereas older age-groups are not subject to similar kinds of institutional control.

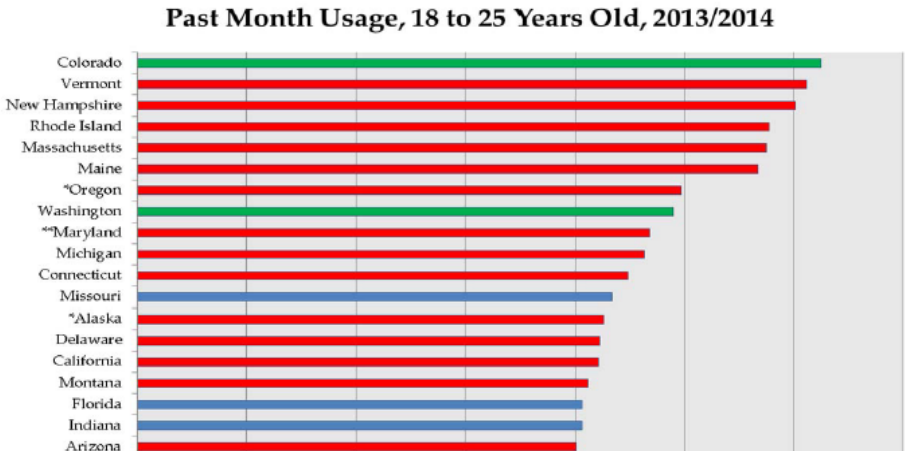
College-age use rose by 17%

Against increases of 2% nationally, use of cannabis by those of college age rose by 17% within the first year of legalised cannabis use.

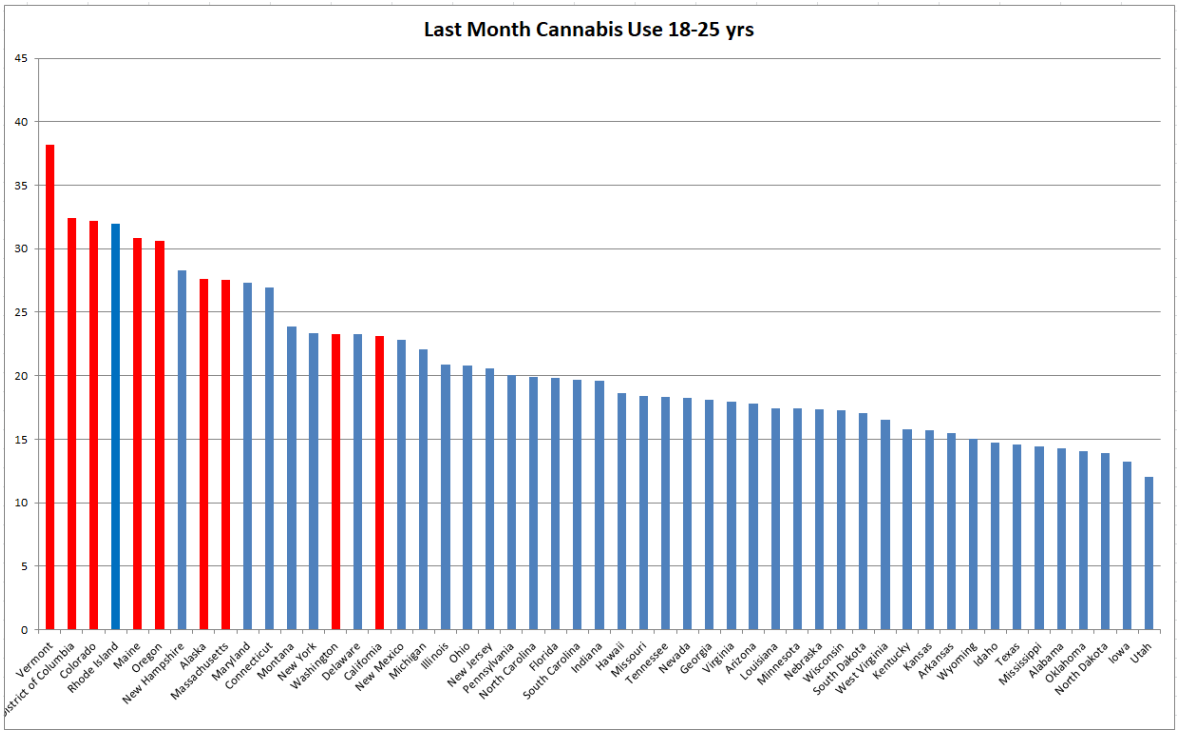


SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014

In 2013/14 Colorado college-age students ranked #1 for cannabis use in the United States, up from #3 in 2011/12 and from #8 in 2005/6.

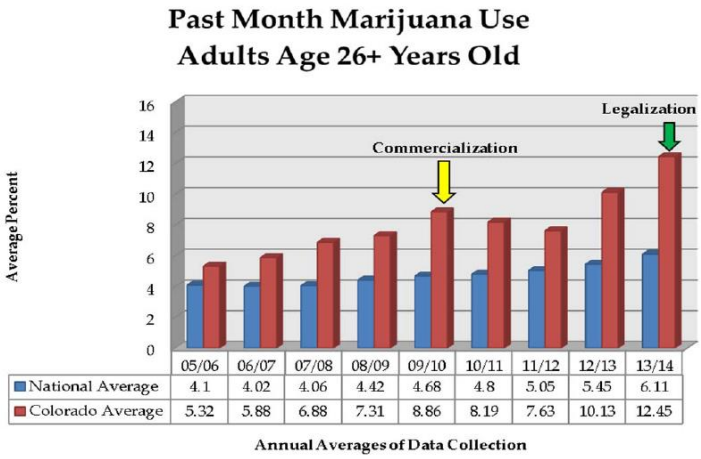


In 2015/16 against increases of 6% nationally, use of cannabis by those of college age rose by 3% (from 31.24% to 32.20%) between 2013/2014 and 2015/2016. In 2015/2016 Colorado college-age students ranked #3 for cannabis use in the United States. States ranking #1 (Vermont) and #2 (District of Columbia) were states that had legalised cannabis or were in the process of legalising (denoted by red below).



Notably, adult use rose by 63%

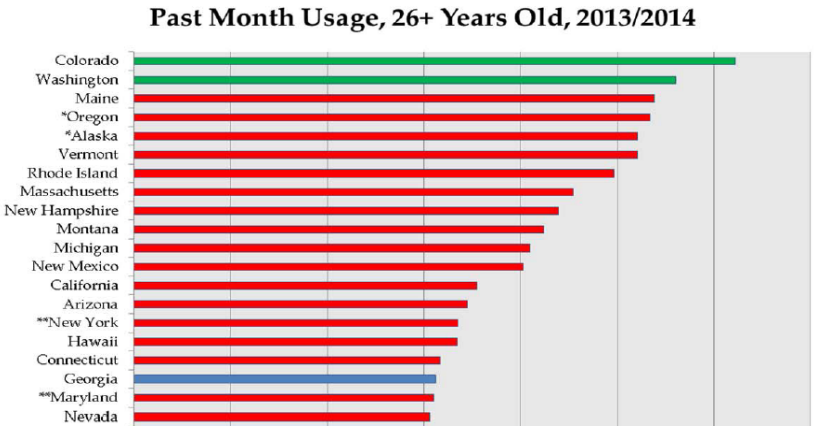
Adult use increased by an alarming 63% in the first year after legalisation against increases of 21% nationally.



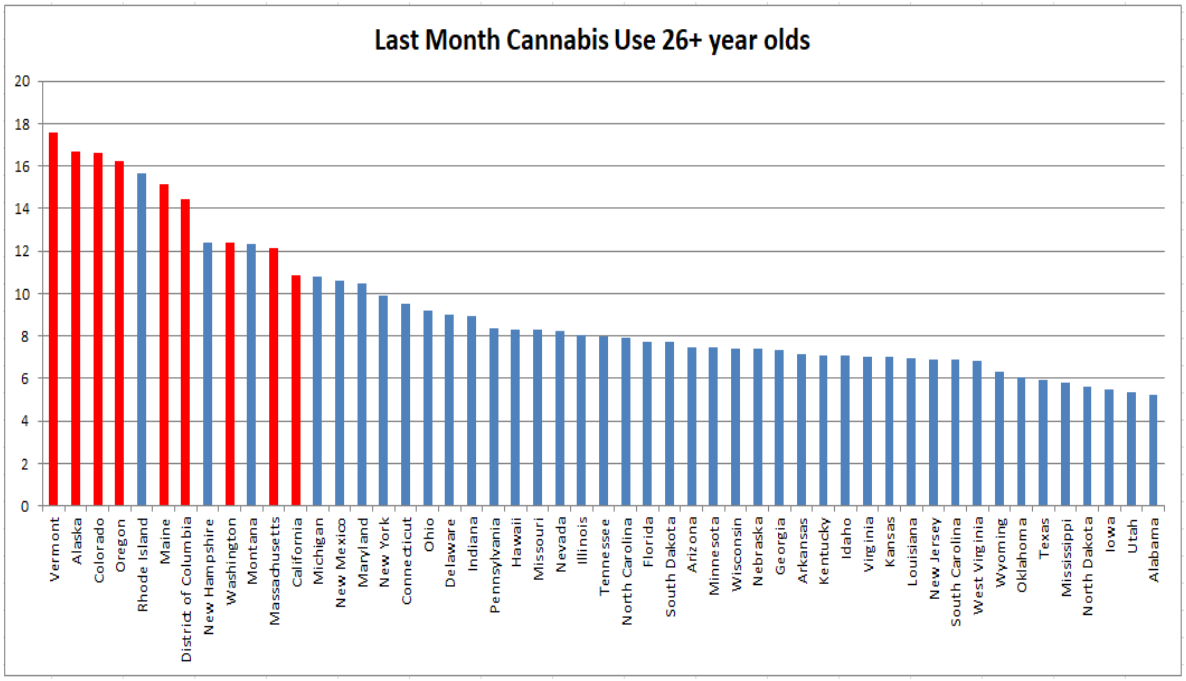
	05/06	06/07	07/08	08/09	09/10	10/11	11/12	12/13	13/14
National Average	4.1	4.02	4.06	4.42	4.68	4.8	5.05	5.45	6.11
Colorado Average	5.32	5.88	6.88	7.31	8.86	8.19	7.63	10.13	12.45

SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2013 and 2014.

In 2013/14 Colorado adults ranked #1 for cannabis use in the United States, up from #7 in 2011/12 and from #8 in 2005/6. States marked red are those states that had legalised cannabis for medical use.



In 2015/16 adult use increased by 33% (from 12.45% - 16.62%) against increases of 49% nationally. In 2015/2016 Colorado adults ranked #3 in the United States. The impact of various states legalising cannabis can be seen on the United States' skyrocketing consumption. States ranking #1 (Vermont) and #2 (Alaska) ahead of Colorado were states which had legalised cannabis or were in the process of legalising (denoted by red below).



Cannabis legalisation, as has been graphically shown, creates considerably more use, not less use as Australians want.

Cannabis-related road fatalities rose by 62%

Road fatalities related to cannabis use rose by 62%, from 71 to 115 persons in the two years following 2014 when recreational cannabis use was legalised.

Traffic Deaths Related to Marijuana*			
Crash Year	Total Statewide Fatalities	Fatalities with Operators Testing Positive for Marijuana	Percentage Total Fatalities (Marijuana)
2006	535	37	6.92%
2007	554	39	7.04%
2008	548	43	7.85%
2009	465	47	10.10%
2010	450	49	10.89%
2011	447	63	14.09%
2012	472	78	16.53%
2013	481	71	14.76%
2014	488	94	19.26%
2015	547	115	21.02%

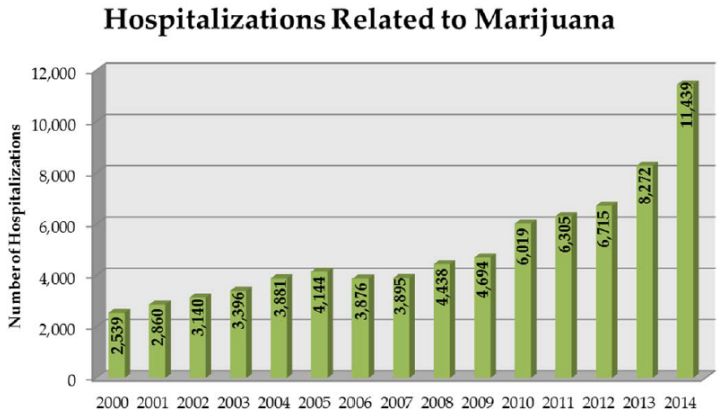
*Fatalities Involving Operators Testing Positive for Marijuana

SOURCE: National Highway Traffic Safety Administration, Fatality Analysis Reporting System (FARS)

Hospitalisations related to cannabis use rose markedly

The number of hospitalisations likely related to cannabis increased 32% in the two year average (2013-14) since Colorado legalised recreational marijuana compared to the two-year average prior to legalisation (2011-2012).

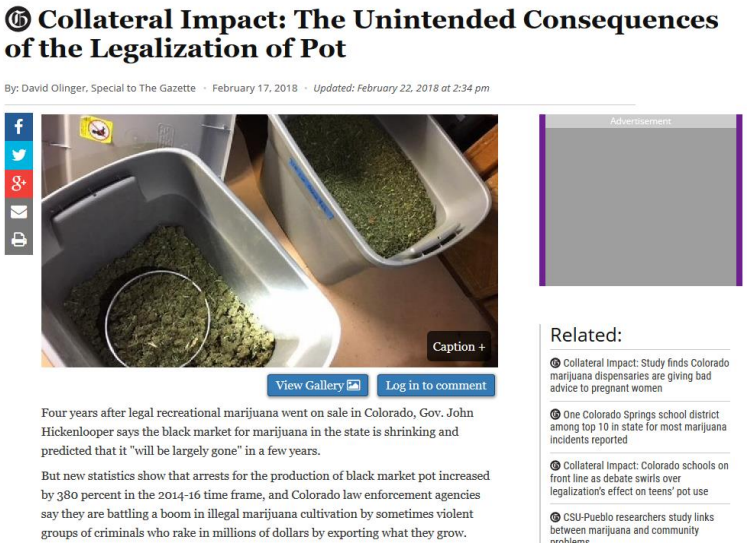
Hospitalisations moved from 6,715 to 11,439 since 2013.



SOURCE: Colorado Hospital Association, Hospital Discharge Dataset. Statistics prepared by the Health Statist and Evaluation Branch, Colorado Department of Public Health and Environment

Legislation introduced to cut black market criminality

Governor Hickenlooper introduced House Bill 1221 in 2017 to address the 380% rise in arrests for black market grows between 2014 and 2016 – see below.



Collateral Impact: The Unintended Consequences of the Legalization of Pot

By: David Olinger, Special to The Gazette · February 17, 2018 · *Updated: February 22, 2018 at 2:34 pm*

Caption +

View Gallery | Log in to comment

Four years after legal recreational marijuana went on sale in Colorado, Gov. John Hickenlooper says the black market for marijuana in the state is shrinking and predicted that it "will be largely gone" in a few years.

But new statistics show that arrests for the production of black market pot increased by 380 percent in the 2014-16 time frame, and Colorado law enforcement agencies say they are battling a boom in illegal marijuana cultivation by sometimes violent groups of criminals who rake in millions of dollars by exporting what they grow.

Related:

- Collateral Impact: Study finds Colorado marijuana dispensaries are giving bad advice to pregnant women
- One Colorado Springs school district among top 10 in state for most marijuana incidents reported
- Collateral Impact: Colorado schools on front line as debate swirls over legalization's effect on teens' pot use
- CSU-Pueblo researchers study links between marijuana and community

http://gazette.com/collateral-impact-the-unintended-consequences-of-the-legalisation-of-pot/article/1621232

House Bill 1220 would aid law enforcement in detecting black market operations and might eliminate Colorado's dubious distinction as the best place in North America to produce pot for widespread distribution. It would limit grows on residential property to 12 plants, with an exception for medical marijuana patients or primary caregivers in compliance with local laws that allow exceptions.

House Bill 1221 would establish an annual $6 million grant program to reimburse local governments for training, education and enforcement related to black market grows. These bills may not go far enough, and the $6 million in HB 1221 does not approach what local authorities need. But the two bills are a good start in what should be an urgent effort to stop the unseemly and dangerous proliferation of black market pot.

http://gazette.com/editorial-pass-bills-to-curb-black-market-marijuana-in-colorado/article/1598339

Colorado added 245,000 extra cannabis users in 5 years

From 2010, when Colorado introduced the commercialisation of medical cannabis (with an explosion of medical cannabis user numbers) to 2015, the state added 245,000 extra frequent cannabis users. This is a **43% increase** in cannabis use during those years for all surveyed age-groups.

Year	Population	Frequent Users
2010	5,029,196	573,919
2015	5,448,055	819,179
Change		245,260

245,000 extra users became susceptible to these cannabis harms

While the harms of cannabis have not been studied for as many years as the harms of tobacco and alcohol, it is already well-established that cannabis combines the harms of intoxication from alcohol with the particulate damage of tobacco. Cannabis presents a wide variety of additional harms which are detailed in Section 2 of this submission.

Medical cannabis ineffective for chronic pain

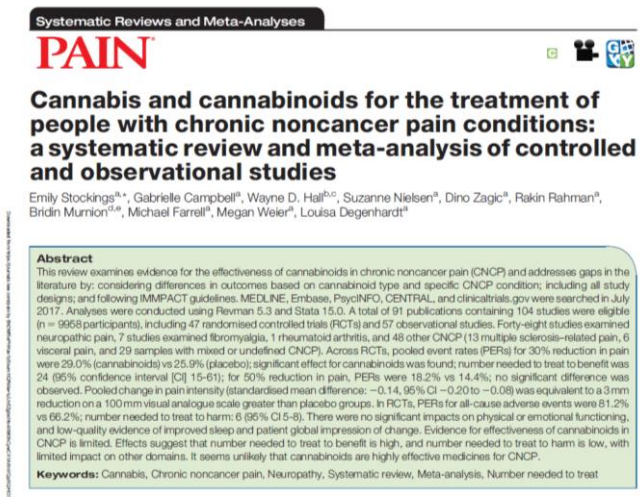
Medical cannabis is chiefly used in Australia and the US for patients who claim that it is needed to combat chronic pain. **But the science is very clear that cannabis is ineffective in and of itself for the alleviation of chronic pain.**

The most extensive 2018 review of the effectiveness of medical cannabis on chronic pain in the online medical journal *Pain* examined 103 journal studies comprising almost 10,000 chronic noncancer pain (CNCP) patients. The review found that at a 30% pain reduction threshold medical cannabis was only marginally more effective than placebo.

The conclusion for the study read as following,

> It seems unlikely that cannabinoids are highly effective medicines for CNCP. There is moderate- to high-grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-related pain. However, NNTBs were high and NNTHs low, with high rates of dropout for AEs, and long-term efficacy and safety is unknown. We also found minimal evidence that cannabinoids are effective in improving other important domains in people with CNCP such as emotional and physical functioning. **Cannabinoids are unlikely to be a monotherapy for CNCP**. People living with CNCP often have complex comorbidities,9,70 and multidisciplinary treatment that includes physical and psychological therapy rather than reliance on medicines alone is likely to be most effective.

Clearly, this extensive study found that cannabis is useful only as an adjunct therapy. This has major implications for prescribing, as well as for the TGA oversight of applications within Australia.



Systematic Reviews and Meta-Analyses

PAIN

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

Abstract

This review examines evidence for the effectiveness of cannabinoids in chronic noncancer pain (CNCP) and addresses gaps in the literature by: considering differences in outcomes based on cannabinoid type and specific CNCP condition; including all study designs; and following IMMPACT guidelines. MEDLINE, Embase, PsycINFO, CENTRAL, and clinicaltrials.gov were searched in July 2017. Analyses were conducted using Revman 5.3 and Stata 15.0. A total of 91 publications containing 104 studies were eligible (n = 9958 participants), including 47 randomised controlled trials (RCTs) and 57 observational studies. Forty-eight studies examined neuropathic pain, 7 studies examined fibromyalgia, 1 rheumatoid arthritis, and 48 other CNCP (13 multiple sclerosis-related pain, 6 visceral pain, and 29 samples with mixed or undefined CNCP). Across RCTs, pooled event rates (PERs) for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo); significant effect for cannabinoids was found; number needed to treat to benefit was 24 (95% confidence interval [CI] 15-61); for 50% reduction in pain, PERs were 18.2% vs 14.4%; no significant difference was observed. Pooled change in pain intensity (standardised mean difference: −0.14, 95% CI −0.20 to −0.08) was equivalent to a 3 mm reduction on a 100 mm visual analogue scale greater than placebo groups. In RCTs, PERs for all-cause adverse events were 81.2% vs 66.2%; number needed to treat to harm: 6 (95% CI 5-8). There were no significant impacts on physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change. Evidence for effectiveness of cannabinoids in CNCP is limited. Effects suggest that number needed to treat to benefit is high, and number needed to treat to harm is low, with limited impact on other domains. It seems unlikely that cannabinoids are highly effective medicines for CNCP.

Keywords: Cannabis, Chronic noncancer pain, Neuropathy, Systematic review, Meta-analysis, Number needed to treat

The US rort of claiming medical cannabis for pain

US statistics show how recreational users have been able to use medical cannabis availability for self-reported 'pain' to feed their recreational use. For instance, 90% of medical cannabis patients in Arizona claim pain as their malady, while 4% use it for cancer.[i] In Colorado, it is 94% for pain and 3% for cancer,[ii] while in Oregon 94% claim to use it for pain.[iii] Only 2% of patients across 7 US states in 2014 used cannabis for verifiable illnesses such as AIDS wasting or MS.[iv]

Drug Free Australia notes that there are no laboratory tests for pain, which makes it a prime candidate for ruse and deception due to its subjective nature and the impossibility of objectively verifying or disproving it.

There are well established profiles for patients of chronic pain across all Western countries, where patients are more predominantly women and those aged 60 and above. For instance, a 2001 study by Sydney University's Pain Management Research Centre found 54% of patients were women, with men suffering in their sixties and women in their eighties.[v]

Yet the profile for medical cannabis pain patients in the USA is very different. A 2007 study of 4,000 medical cannabis patients in California found that their average age was 32, three quarters were male and 90% had started using cannabis while teenagers,[vi] an identical age and gender profile to that of recreational users across the US.[vii]

This discordant profile means that medical cannabis in the various states of the US has mainly amounted to a quasi-legalisation strategy for recreational use of cannabis via subterfuge and ruse.

Inquiry must examine cannabis use for chronic pain

This State Inquiry must ask the question as to why medical cannabis is so popularly used for a condition for which it is relatively ineffective. If medical cannabis in Australia is being used for feigned chronic pain as a way of accessing cannabis preparations for de facto legalised recreational use, then Western Australia has the opportunity, via this Inquiry, of taking the Australian lead in publicising that a voluminous science does not support the use of cannabis for chronic pain. TGA spreadsheets show that 61% of Australians are using cannabis for chronic pain and know nothing of the newly-established harms

[i] Arizona Department of Health Services (Apr. 14, 2011-Nov. 7, 2012) Arizona Medical Marijuana Act Monthly Report
[ii] Colorado Department of Public Health and Environment (Dec. 31, 2012) Medical Marijuana Registry Program Update
[iii] Oregon Health Authority (Oct. 1, 2014) "Oregon Medical Marijuana Program Statistics
[iv] Kevin Sabet et al. "Why do people use medical marijuana? The medical conditions of users in seven U.S. states" The Journal of Global Drug Policy and Practice (Volume 8, Issue 2 Summer 2014)
[v]] Blyth et al. "Chronic Pain in Australia: A prevalence study" (Jan. 2001) Pain
[vi] Thomas J. O'Connell and Ché B Bou-Matar (Nov. 3, 2007) Long term marijuana users seeking medical cannabis in California (2001-2007): demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. Harm Reduction Journal
[vii] Gogek, Ed (2015-08-03). Marijuana Debunked: A handbook for parents, pundits and politicians who want to know the case against legalization pp104,5. InnerQuest Books

of cannabis in relation to cancer and birth defects. They have a right to know, as historically shown with tobacco, and Western Australia must take the lead.

CENTRAL ISSUES FOR THE WA CANNABIS INQUIRY – 4

The UK recognises the limitations of cannabis on chronic pain and advises it only as a last resort

UK more conservative than Australia on demonstrated benefits

Because the United Kingdom's public is better versed in the real harms of cannabis due to a more proactive BBC, the UK takes a more conservative stance on cannabis, insisting on the rigour of clinical trials for any medical indication, with no access to medical cannabis without a trial.

Drug Free Australia has previously recommended a similar Australian regulatory skepticism to that of the UK in regards to requests for medical cannabis as a sole treatment for chronic pain. The UK approach is explained in the media article below.

As per https://www.christian.org.uk/news/doctors-told-dont-give-out-cannabis-based-drugs-for-chronic-pain/,

Doctors told: Don't give out cannabis-based drugs for chronic pain

Cannabis-based drugs should not be prescribed to manage chronic pain, draft official guidance says.

The National Institute for Health and Care Excellence (NICE) made the draft recommendation after finding the "potential benefits offered were small compared with the high and ongoing costs".

The guidance follows concerns about medical cannabis from senior medical experts including the head of NHS England.

None recommended

NICE said its recommendations were focused on understanding the drugs' safety and cost effectiveness.

It considered the use of cannabis-based products for chronic pain, spasticity in people with multiple sclerosis, chemotherapy-induced nausea and severe epilepsy.

While it did recommend considering one such drug for a specific type of vomiting, no cannabis-based drugs were recommended for pain or spasticity. NICE called for more research on epilepsy.

'Lacking'

Paul Chrisp, a senior director at NICE, said before the analysis the organisation believed a "robust evidence base for these mostly unlicensed products was probably lacking".

"Having now considered all the available evidence it's therefore not surprising that the committee has not been able to make many positive recommendations about their use."

Dr Keith Ridge, Chief Pharmaceutical Officer at NHS England, said related recommendations released by the NHS "aim to help us develop the evidence base to understand how safe these products are".

'Mistake'

In May, the head of NHS England warned that medical cannabis risks "normalising drug use" in the UK.

Simon Stevens said: "I think we have to be careful, as we have a legitimate national debate on medical cannabis, that we don't look back in a decade's time and wonder whether we inadvertently made a big mistake."

Dame Sally Davies, England's Chief Medical Officer, warned in March that people believed medicinal cannabis can cure multiple illnesses but it should only be prescribed as a "last resort".

CENTRAL ISSUES FOR THE WA CANNABIS INQUIRY – 5

Current costs of using medical cannabis are directly comparable to costs when it was illegally obtained

Cost of pharmaceutical cannabinoids identical to illegal cannabis in Australia

The cost of cultivated **crude** cannabis in the United States for medical cannabis patients was about $500 per month as is reflected by NORML in the US in its 2009 Recommendations to the Obama Administration on marijuana dispensaries, which stated that,

There is little doubt as to why cannabis dispensaries are multiplying at such a rate. The price of cannabis in dispensaries ranges from $12.50 to $25 per gram (28 grams per ounce). The average “medical” user with a chronic medical condition may consume from 1.5 to 3.0 grams per day.31 Therefore, the monthly cost to patients **ranges from $562 (1.5 grams/day at $12.50/gm) to $2,250 (3 grams/day at $25/gm).** Since the herbal cannabis, which is of varying strains and quality, has not received FDA approval, none of this expense is covered by a patient’s health insurance, and there is no assurance of quality control or accurate dosage information.
http://norml.org/pdf_files/Marijuana_Dispensaries_Recommendations.pdf

This presents the same cost to patients as purchasing illegal cannabis from a dealer, which in 2015, before medical cannabis legislation was completed in Australia, was between $12.00 and $12.50 a gram.

Sativex, by comparison, cost on average $500 per month for New Zealanders back at that time - see page 38 of the NSW General Purpose Standing Committee No. 4 Report – The Use of Cannabis for Medical Purposes.
http://www.parliament.nsw.gov.au/prod/parlment/committee.nsf/0/fdb7842246a5ab71ca257b6c0002f09b/$file/final%20report%20-%20the%20use%20of%20cannnabis%20for%20medical%20purposes.pdf

It is clear that any patient currently purchasing cannabis in Australia is paying no more than if they were purchasing illegally grown cannabis. Drug Free Australia recommends that the WA Government not be misled about the comparability of medical cannabis costs.

Cost must be brought down via efficiencies, but not by relativising TGA standards

Given that the medical landscape has dramatically moved with the cancers and birth defects caused by cancer making it no longer viable as a general medical treatment, the current call by cannabis activists is to relativise TGA standards for the sake of cutting costs. For the very small number of conditions that only medical cannabis can treat such a call would never be acceptable for any other medicine available in Australia and should be rejected on that ground alone.

Illegal tinctures and oils already abound despite the legal provision of medical cannabis, but those who provide them are not bound to quality control or the higher costs of regulation and security, nor of clinical trials, which is entirely unfair to those companies that abide by the regulatory frameworks. The Australian Government is bound to defend those abiding by law, and the TGA should pursue any illegal manufacture of medical cannabis products being sold to Australians.

Federal and State governments should nevertheless attempt to reduce costs via efficiencies and economies of scale, but never relativise regulations and rigour where they currently exist.

CENTRAL ISSUES FOR THE WA CANNABIS INQUIRY – 6

Cannabis clinics in Sydney agree there are no major impediments to obtaining medical cannabis

Access to medical cannabis adequate according to clinics

In mid-August 2019 Drug Free Australia spoke with the management of two cannabis clinics, one in the Sydney CBD and the other in North Sydney. Drug Free Australia also spoke with an in-house doctor of one of those clinics.

The discussions were in response to claims on the Channel 7 Sunday Night program early in August that medical cannabis was very difficult to access for needy Australians.

Responses from both clinics were the same, that access to medical cannabis was much improved over the previous 12 months, with streamlining of Federal and State requirements. To the question of what conditions would not pass muster with an Open Access application to the TGA the answer was that the TGA was very amenable if due cause could be demonstrated and they expected no problem for any verifiable condition. The clinics agreed that the bar was not set too high in their estimation. Their advice was entirely at odds with the claims of the Channel 7 program, and this must be carefully noted by the WA Cannabis Inquiry.

Further discussion with one of the clinics highlighted the importance of having a patient's GP involved in the prescription of cannabis, given that a patient's GP best knows what other medications have been prescribed. This local GP information is vital to a clinic's onsite doctors who need to be very aware of negative interactions between medications, amongst other things. Drug Free Australia has previously warned against Australia adopting the 'pot doctor' approach of some US States, whereby 90% of prescriptions are written by a handful of doctors.

Drug Free Australia again has urged that the Federal Government not be deterred from ensuring that cannabis is treated like every other medicine regulated by the TGA. **Attempts to relativise regulatory frameworks are in most instances going to be driven by pot activists whose endgame goal is the legalisation of home-grown cannabis for medical purposes, with the longer term goal of legalised recreational use.** The WA Inquiry is asked to support these calls.

APPENDICES

1. **Daily mail news article – Cannabis the new Thalidomide?**
2. **Chromothripsis the mechanism for genotoxic and mutagenic nature of cannabis**
3. **Birth Defects study**
4. **Pediatric Cancer study**

Daily Mail
AUSTRALIA

Could medical cannabis be the new THALIDOMIDE? Fears of a crisis as doctors consider doling marijuana-based medicines out to pregnant mothers despite evidence the drug can damage foetuses

- **Pressure to loosen NHS guidelines on medical cannabis use is growing in the UK**
- **The British Medical Journal warned that widespread use could lead to disaster**
- **The potential crisis was compared to the thalidomide scandal of the 50s and 60s**

By Guy Adams for the Daily Mail

Published: 10:31 AEST, 24 November 2018 | Updated: 05:36 AEST, 28 November 2018

Each of the 400 phone calls to the cannabis dispensaries followed a script. 'Hi,' said a female voice. 'I'm eight weeks pregnant and feeling really nauseated. Are there any products recommended for morning sickness?'

In two-thirds of cases, the reply was: 'Yes'.

Around half of those callers who'd received an affirmative answer were then advised to buy a specific 'cure' in a form they could eat.

Just under 40 per cent were told to get it in a form that could be inhaled or smoked. Most of the remainder were offered tinctures or drinks.

The recommended cure in question? Marijuana. But far from being genuine requests for help from expectant mothers, the phone calls were part of a research project by the University of Colorado.

The researchers were pretending to be pregnant to see how cannabis — legal for medical reasons in the U.S. state of Colorado since 2000 and fully legal since 2014 — was being dispensed. The answers they received offer a worrying insight into the booming medical marijuana industry.

When 400 phone calls were made to cannabis dispensaries from a supposedly pregnant woman, two thirds recommended cannabis products for morning sickness (stock image)

‘After eight weeks [of pregnancy], everything should be good with consuming alcohol and weed,’ one dispensary assistant replied.

‘When I was pregnant and started to feel nauseous, I did not smoke [cannabis] more than two times a day,’ recommended the proprietor of another clinic.

‘Edible [marijuana] would not hurt the child,’ reassured another, telling the woman, wrongly, that something ‘going through your digestional tract’ will have no effect on an unborn child.

Of the 277 dispensaries that recommended cannabis as a cure for morning sickness, three-quarters then attempted to sell a version of the drug containing THC, the chemical that gives users a ‘high’.

Many also advised their pregnant patients to keep their consumption of this intoxicating drug secret from their doctor.

‘The doctor will probably just tell you that marijuana is bad for kids and try pushing pills on you,’ said one. ‘I do not know if the baby doctors are chill or not, [so] do not go stoned when you talk to them,’ warned another.

Perhaps those doctors had good reason for their reservations about cannabis. For the Colorado research paper, published in the journal Obstetrics and Gynaecology earlier this year, highlights cannabis as a matter of growing concern to medical practitioners across the world.

Increasingly, marijuana is being sold for medical reasons. Yet this ‘medical’ marijuana is very far from being the safe, natural healthcare product its often-rapacious suppliers would have us believe.

‘After eight weeks [of pregnancy], everything should be good with consuming alcohol and weed,’ one dispensary assistant said (stock image)

In some circumstances, the product — which is becoming legal in growing numbers of countries, including Canada, the U.S. and most recently Britain in highly specific circumstances — can be dangerous and possibly fatal. Particularly when taken by pregnant women.

To blame is a simple fact: a multitude of studies over several years have shown all forms of cannabis to be ‘teratogenic’. Meaning that, like tobacco or excessive alcohol, they can harm a foetus.

The drug has been linked to a host of serious birth defects, including at least six life-threatening deformities.

They include two congenital heart problems; a neurological condition called anencephaly, in which a child is born with a large portion of the brain missing, often dying within hours; and the birth defect gastroschisis, where the intestines develop outside the body.

‘Babies exposed to marijuana in utero are at increased risk of admission to neonatal intensive care units,’ says Torri Metz, a University of Utah professor who was among the Colorado study’s authors.

‘There are also concerns about possible long-term effects on the developing brain, impacting cognitive function and decreasing academic ability later in childhood.’

Which brings us to the situation in Britain, where there is pressure on the Government from an increasingly powerful cannabis lobby to loosen the NHS guidelines on medical cannabis use.

In Britain, there is pressure on the Government from an increasingly powerful cannabis lobby to loosen the NHS guidelines on medical cannabis use (stock image, cannabis oil)

They were relaxed this year following two high-profile cases involving children who suffer from serious forms of epilepsy.

One, Alfie Dingley, found an unlicensed, technically illegal cannabis oil from Holland prevented his seizures. Another, Billy Caldwell, had medical marijuana from Canada confiscated at customs, causing him to be admitted to hospital with what his family described as ‘life-threatening’ seizures.

In response to the public outcry over both cases, the Home Office relaxed the law to allow specialist doctors to prescribe unlicensed cannabis-based drugs to patients.

Their use is still limited to three distinct conditions: epilepsy, nausea associated with chemotherapy, and muscle stiffness associated with multiple sclerosis. Even then, patients must first have tried conventional medicines.

But the cannabis lobby is calling for it to be made more widely available, claiming six million Britons would eventually use the product for a variety of ailments, including pain and nausea relief. It would almost certainly mean dispensaries handing it out over the counter, just like in Colorado.

The British Medical Journal (BMJ) recently published an article arguing that the widespread use of medical cannabis could eventually lead to a public health crisis bearing comparison with the thalidomide disaster.

‘When I was pregnant and started to feel nauseous, I did not smoke [cannabis] more than two times a day,’ recommended the proprietor of another clinic (stock image)

That scandal, one of the most notorious in modern history, came after the drug thalidomide was given to large numbers of pregnant women from the late Fifties to the early Sixties, mostly to treat morning sickness.

It caused hundreds of thousands of miscarriages, and resulted in around 10,000 babies being severely deformed. Many died.

‘Thalidomide was marketed for anxiety, morning sickness and pain relief. Very similar claims are now being made about cannabis, and we are being told that millions of people should take it,’ says the author of the BMJ article, Dr Albert Reece, a professor of medicine at Edith Cowan University in Perth, Australia.

‘But as with thalidomide, no one is properly looking at the side-effects. They are frightening.

‘During foetal development, the presence of it increases the chances of a child developing heart and intestinal defects. In the womb, it can also not only interfere with brain development but basically amputate the forebrain.’

Even for adults, there are serious side-effects, he adds: ‘Cannabis is linked to serious psychiatric symptoms, including depression, anxiety, bipolar disorder and schizophrenia. Plus stroke, heart attack and 12 kinds of cancer.’

The cannabis doctors can now prescribe in Britain — albeit only to certain very sick patients — can have intoxicating levels of the chemical THC. Most British patients who will take it are expected to be given it in the form of capsules or a highly concentrated oil. However, chemically speaking, there will be very little to distinguish these medical products from what recreational cannabis users might smoke.

For example, Bedrocan, a Dutch-made brand which is one of the world’s most popular varieties of medical cannabis, contains 22 per cent THC according to its manufacturer’s website, making it more intoxicating even than the ‘skunk’ (which ranges from around 14 per cent to 20 per cent THC for ‘superskunk’) that illegal dealers sell.

The difference, says the manufacturer, is that Bedrocan — which consists purely of dried cannabis flowers — is chemically standardised, so it is easier to regulate dosage, when taking the product.

Meanwhile, in California, where medical cannabis was first made available 20 years ago and has since been entirely legalised, a high-profile organisation called ‘Cannamommy’ advertises a range of what it terms ‘safe, organic natural products’ designed for mothers. One popular brand of medical marijuana is called ‘Trainwreck’, advertised as a cure for migraines, pain and arthritis.

In California, where medical cannabis was first made available 20 years ago and has since been entirely legalised, a high-profile organisation called ‘Cannamommy’ advertises a range of what it terms ‘safe, organic natural products’ designed for mothers (stock image)

According to the maker, the product, which is between 12 and 21 per cent THC and is sold in a dried form suitable for smoking, ‘begins its hurtle through the mind with a surge of euphoria, awakening creativity and happiness’.

Another Cannamommy product, ‘Green Crack’, which it recommends for housewives suffering ‘fatigue, stress and depression’, induces ‘an invigorating mental buzz’. A third, ‘Guerilla Glue’, will apparently ‘deliver heavy-handed euphoria and relaxation, leaving you feeling glued to the couch’.

To critics, this sales patter suggests many customers are as interested in enjoying a legal high as they are the medical benefits.

And when medical marijuana products are aimed at mothers, it’s a dangerous trend, they argue.

‘We are at ground zero of this new medical epidemic, which will lead to havoc,’ says one critic, Karen Randall, an emergency room physician in Colorado. ‘The number of babies testing positive for THC has increased dramatically.’

Randall says her local area contains 15 medical cannabis dispensaries. ‘When a breast-feeding mother uses marijuana, it gets concentrated in the breast milk.

‘There are many studies that show memory is decreased with constant use, so I guess that in five to ten years, we are going to see a lot of kids with learning issues.’

Someone who illustrates the potential hazards is Marie McKillop, 36, from the Australian city of Brisbane, who says smoking marijuana during pregnancy led to her daughter’s death.

This ‘medical’ marijuana is very far from being the safe, natural healthcare product its often-rapacious suppliers would have us believe (stock image)

Her baby, named Crystal, weighed just 2lb 9oz at birth and was unable to breathe or feed unaided because of a serious congenital heart defect. She underwent three major heart surgeries, but died aged eight months.

Adding to her mother’s trauma was the fact she’d previously had four miscarriages. ‘I felt totally broken,’ Marie says.

At the time the tragedy occurred, several years ago, McKillop was a troubled young woman battling substance abuse problems.

Though clinicians advised her to steer clear of the hardest illegal narcotics, they concluded that she should continue to take marijuana while pregnant. ‘The fear was that if I stopped, it would give me withdrawal symptoms, which could make me miscarry,’ she recalls.

Later, in hospital reports, marijuana was described as a ‘high contributing factor’ to Crystal’s subsequent health problems.

Thankfully, having weaned herself off drugs, Marie has since had three healthy children.

Others won’t be so lucky.

Her doctor, Stuart Reece, believes the drug affects three key organs of an unborn child: the brain, the heart and the intestines.

He cites a study in the Toxicology Journal last year in which pregnant laboratory mice were exposed to cannabis, which found that ‘smoking marijuana during pregnancy even at low doses can be embryotoxic and fetotoxic’; and a University of Arkansas study also from 2017 which associated pre-natal cannabis exposure with ‘lower birth weight, life-long smaller head circumference, reduced length of gestation, neonatal neurological disturbances, [and] reduced function in specific cognitive domains’.

Two studies by the American Center for Disease Control have linked it to anencephaly, while the American Heart Association and American Academy of Pediatrics believe it increases rates of ventricular septal defect and Ebstein’s anomaly, two heart defects.

The drug's links to gastroschisis — when the intestines develop outside the body — are documented by, among others, a long-running Canadian study and a Hawaiian research project which has linked cannabis to no fewer than 21 birth defects.

'Only once has a known teratogen like cannabis been marketed globally,' Dr Reece says.

'That was thalidomide. It's the reason we have the entire modern drug approval system, but the medical cannabis lobby is saying that system should be abandoned and the drug should be given to millions of people. It's incredibly dangerous.'

Sharing this view are 166 of Britain's most eminent pain relief doctors. Last month, they wrote to The Times, saying medical cannabis 'will provide little or no long-term benefit in improving pain and may be associated with significant long-term adverse cognitive and mental-health detriment.'

Until this year's relaxation in the law, drugs in Britain that are made from cannabis had an identical status to those derived from other illegal narcotics such as heroin (stock image)

They argued there is no medical evidence that, in this field, cannabis works. There are, however, serious psychological problems associated with its regular use.

The 166 doctors cited a report from the International Association for the Study of Pain, which took in the results of 104 studies.

The report concluded that 24 patients in pain would need to be treated for just one to experience any benefit.

Yet one in six would suffer some form of 'harm' due to side-effects, including nausea, dizziness, insomnia and depression.

And the report concluded: 'It seems unlikely cannabinoids are highly effective medicines for chronic non-cancer pain.'

'As doctors, the first law is to "do no harm",' says author Dr Raj Munglani, a chronic pain expert who practises in Cambridge and London. 'We could end up damaging more people than we help. We fear new rules in the UK could cause a major public health crisis.'

Until this year's relaxation in the law, drugs in Britain that are made from cannabis had an identical status to those derived from other illegal narcotics such as heroin.

To be licensed for medical use, these products must undergo stringent testing to ensure that they are effective and safe.

Though the licensing process takes several years, it's perfectly possible to negotiate it.

The UK firm GW Pharmaceuticals has done just that with marijuana, developing two licensed drugs: Sativex (with moderate levels of THC) which treats spasticity associated with multiple sclerosis, and Epidolex, for epilepsy (interestingly, patient notes make clear that they must never be taken by pregnant women).

In theory, there's never been anything to stop other advocates of medical cannabis developing licensed products in this way to combat the myriad other conditions they say it can treat. But none have so far succeeded.

It seems it's far easier to lobby politicians to relax the licensing laws. But the danger is that this could one day lead to a situation in Britain where, as in Colorado, cannabis is sold as a cure for morning sickness — with potentially terrifying consequences.

Mutation Research 789 (2016) 1–11

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity

Albert Stuart Reece*, Gary Kenneth Hulse

School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA 6009, Australia

ARTICLE INFO

Article history:
Received 11 January 2016
Received in revised form 17 April 2016
Accepted 1 May 2016
Available online 4 May 2016

Keywords:
Cannabis
Microtubules
Tubulin
Dose-response relationship
Threshold dose
Population effects
Oncogenesis
Foetal malformations
Chromothripsis
Epigenetics
Transgenerational
Heritable
Interdisciplinary

ABSTRACT

The recent demonstration that massive scale chromosomal shattering or pulverization can occur abruptly due to errors induced by interference with the microtubule machinery of the mitotic spindle followed by haphazard chromosomal annealing, together with sophisticated insights from epigenetics, provide profound mechanistic insights into some of the most perplexing classical observations of addiction medicine, including cancerogenesis, the younger and aggressive onset of addiction-related carcinogenesis, the heritability of addictive neurocircuitry and cancers, and foetal malformations. Tetrahydrocannabinol (THC) and other addictive agents have been shown to inhibit tubulin polymerization which perturbs the formation and function of the microtubules of the mitotic spindle. This disruption of the mitotic machinery perturbs proper chromosomal segregation during anaphase and causes micronucleus formation which is the primary locus and cause of the chromosomal pulverization of chromothripsis and downstream genotoxic events including oncogene induction and tumour suppressor silencing. Moreover the complementation of multiple positive cannabis-cancer epidemiological studies, and replicated dose-response relationships with established mechanisms fulfils causal criteria. This information is also consistent with data showing acceleration of the aging process by drugs of addiction including alcohol, tobacco, cannabis, stimulants and opioids. THC shows a non-linear sigmoidal dose-response relationship in multiple pertinent *in vitro* and preclinical genotoxicity assays, and in this respect is similar to the serious major human mutagen thalidomide. Rising community exposure, tissue storage of cannabinoids, and increasingly potent phytocannabinoid sources, suggests that the threshold mutagenic dose for cancerogenesis will increasingly be crossed beyond the developing world, and raise transgenerational transmission of teratogenicity as an increasing concern.

Contents

* Correspondence to: 39 Gladstone Rd., Highgate Hill, Brisbane, Queensland, Australia.
E-mail addresses: sreece@bigpond.net.au, asreece@bigpond.net.au (A.S. Reece).

http://dx.doi.org/10.1016/j.mrfmmm.2016.05.002
0027-5107/

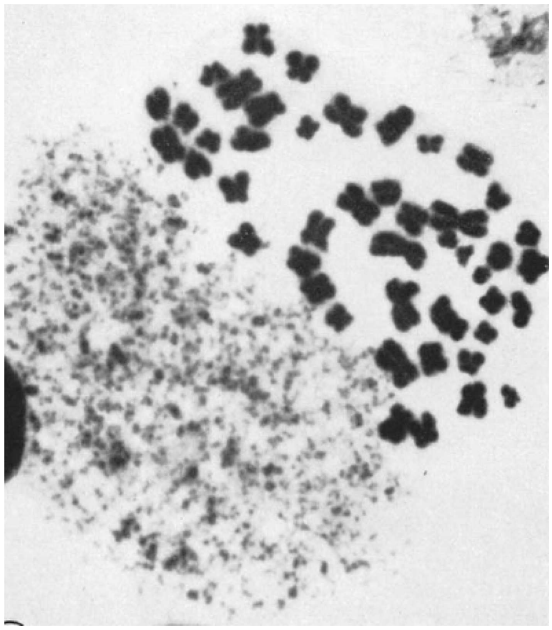


Fig. 1. Chromosomal Pulverization.
Original Report of Chromosomal Pulverization. Figure 7 , Kato H., Sandberg AA (1967). "Chromosome Pulverization in Human Binucleate Cells. Following Colcemid Treatment." J. Cell Biol. 34 (1): 35–45. Re-used by permission.

1. Introduction to seminal paper

In a remarkable and highly celebrated report, the Pellman lab recently showed that severe chromosomal fragmentation involving dozens of double stranded breaks and subsequent apparently random and disordered repair of some of the fragments, could rapidly occur during the DNA synthetic phase (G2 and S-phases) of the mitotic cell cycle, if chromosomes became isolated from the main nuclear mass [1]. In this technical tour de force, high resolution DNA sequencing of single cells and live cell imaging was deployed to show that chromosomes which had become detached from the mitotic spindle or chromosomes became isolated in micronuclei, where, lacking the normal full complement of replication and repair enzymes, the DNA became shattered in the process of disordered and dysregulated replication. Such damage could become propagated through subsequent rounds of cell division, where the isolated chromosomes could also become joined up with those of the main nucleus. Where two or a few chromosomes were trapped together, in such a micronucleus random exchange could occur between them. Chromosome "pulverization" was first described in 1967 due to experimental viral infection [2] (Figs. 1 and 2). The process has recently been named "chromothripsis" for chromosomal shattering at hundreds [3] or thousands [4] of loci; and a milder form was called "chromoplexy" (chromosomal tangles or braids, Fig. 3) [5]. Extraordinarily, this process was shown to proceed as rapidly as within 16 h [1].

This remarkable result immediately resolved a long standing paradox in cancer research as to how such dramatic event could arise when the normal fidelity of DNA replication occurs with an error (mutation) rate of only 10^{-8}, and the rate in germ stem cells is one hundred times lower. It also simultaneously provided an elegant mechanism for the high rate of micronuclei, chromosomal fragments and abnormal chromosomes (truncated arms, chain and ring chromosomes and double minute circles [6]) which are frequently seen in malignant tissues (Fig. 4)[7]. Tetraploidy itself has been shown to increase chromosomal instability, tolerance of mitotic errors and the multidrug resistance typical of transformed and tumour cells and even the anchorage-independent growth of non-transformed cells [7].

In addition to cancer, such chromothriptic events have also been shown in various congenital abnormality syndromes [8–14].

2. Dynamics of the cell cycle

The cell cycle has numerous check points which are designed to prevent such genetically catastrophic events from occurring. The mitotic spindle assembly checkpoint (SAC) in particular requires all chromosomes to be attached to the spindle, and sister replicates to be attached at their kinetochores with opposing polarity (bi-orientation) to bundles of microtubules of the mitotic spindle which will draw them to opposite poles of the cell [15]. Mostly errors in this complicated machinery [16–19] generate cell cycle arrest, apoptosis, or the irreversible entry into cellular senescence [7]. But delay at the SAC is not indefinite [15]. Some cells slip back as tetraploid cells into interphase and a very few escape cell cycle controls altogether. This can particularly occur when chromothriptic events involve the functional silencing of such major tumour suppressor genes as TP53 (P53) and CDKN2A (P16INK4A), which normally sense and amplify such cellular and senescence checkpoints [20]. Other genetic causes (mutations, insertions and deletions) also exist for tumour suppressor gene silencing. Hence the usual outcome of such events at the tissue level is; growth arrest via apoptosis, senescence or cell cycle delay [21], and occasionally malignant transformation where the malignant clone may have a growth advantage [7,22].

The pathway described by the Boston group [1] was therefore inhibition of spindle dynamics/failure of spindle attachment/micronuclear formation/chromosomal shattering or pulverization/haphazard chromosomal annealing by non-homologous end joining or microhomology-mediated break-induced replication, then cell cycle arrest or occasionally and alternatively, oncogenic transformation [3,12,20,22–25]. Chromothripsis has been described as occurring in about 2–3% of cancers including melanoma, sarcoma, lung, thyroid, oesophageal and renal cancers [4], although it is seen much more commonly in cancers of the bone (25%) [20,26], brain (39%) [27,28], bowel [29] and a majority of prostate tumours [5]. It has also been said to be more common in cancer per se, as the technical difficulties in unravelling the enormous complexities in sequencing errors to which it gives rise are only beginning to be probed [5,22,24,26,27,29,30]. Its presence and severity correlate with poor prognostic outcomes [27,30]. Progressive chromosomal instability instigated or assisted by chromothriptic and disorderly mitotic mechanisms also explain the usual tendency of tumours to become increasingly aggressive [26]. Curiously single cell chromothripsis has also been shown on occasion to cure rare genetic disorders [31].

The Boston work [1] also focussed attention on the extraordinarily complicated machinery associated with the microtubules comprising the mitotic spindle. Microtubules are primarily made up of α- and β- tubulin dimers which, together with their numer-

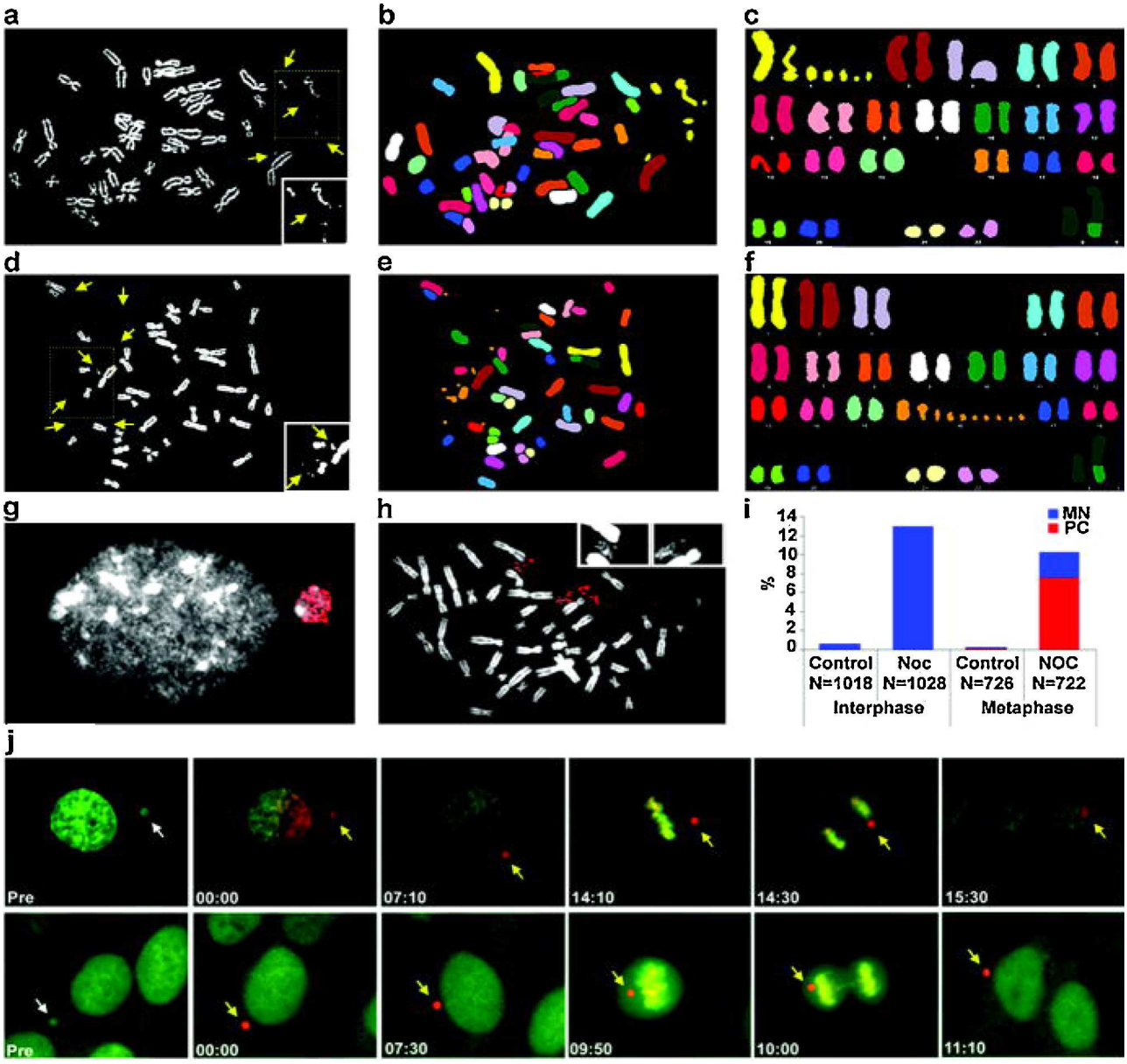


Fig. 2. Chromosomal Pulverization in Micronuclei. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) Caption: Pulverization of chromsome 1 after nocodozole release (a); (b) SKY pseudocolour;
(c) Ordered SKY karyotype; (d)–(f) Pulverization of chromsome 16 similarly imaged (as in (a)–(c).(g) A BrdU positive (red) micronucleus (DNA white); (h) Selective labelling of (red) pulverized Chromsome; (i) Percent cells with intact (blue) or pulverized (red) chromsomes in micronuclei from control or nocodozole released cells. Fate of micronucleus (photoconverted green to red) through Anaphase (Top row) – re-incorporation into primary nucleus; (Bottom row) No re-incorporation.
From: Crasta K, Ganem NJ, Dagher R, Lantermann AB, Ivanova EV, Pan Y, Nezi L, Protopopov A, Chowdury D, Pellman D (2012), "DNA Breaks and Chromsome Pulverization from Errors in Mitosis."Nature 482 (7383): 53–58. Figure 5. Re-used by Permission.

ous associated proteins, are highly polymerized into microtubules which grow ("rescue") and shrink ("catastrophe") and probe the internal cytoplasmic space of the cell, and form the highly dynamic framework ("dynamic instability") upon which the chromosomal separation of anaphase occurs [15,18]. Whilst the microtubules appear to be static on fixed cell fluorescent imaging, in many tissues they are actually lengthening at their plus ends (centrally) whilst simultaneously disassembling at their minus ends at the centriole ("treadmilling") to give rise to an overall poleward flux [15]. In particular the Dana Farber/Harvard studies highlighted the way in which agents which interfere with tubulin polymerization or their dynamic instability can have major downstream ramifications [1]. This result has been shown both for various genetic disruptions [7,32,33] and chemical toxins.

3. Mitotic spindle poisons

The Boston studies used nocodozole to induce cell cycle arrest [1] which acts by binding tubulin subunits and preventing their polymerization [15]. Vincristine, vinblastine and colchicine act similarly [15]. The chemotherapeutic agent taxol acts by binding to and stabilizing microtubules, inhibiting their dynamic instability [15].

Of significance and concern Δ-9 tetrahydrocannabinol (THC) [34–37] and other cannabinoids [38] act similarly to taxol. Importantly it has been shown that a 2 h exposure to 5 and 10 μM of THC reduced tubulin mRNA by 50% & 78% [36]. Recapitulating many of the key features of the above findings, THC has been shown to interfere with tubulin polymerization [34,39], be associated with micronuclear formation (4–6 fold increase) [21,40–45], cause

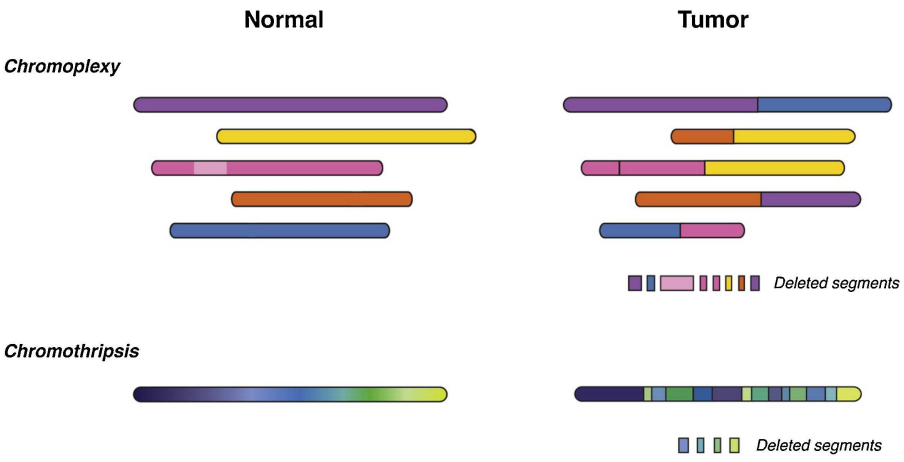


Fig. 3. Diagrams of Chromoplexy & Chromothripsis.
From Figure 1, Shen MM "Chromoplexy: a new category of compex rearrangements in the cancer genome."Cancer Cell 23 (5): 567–569. Re-used by permission.

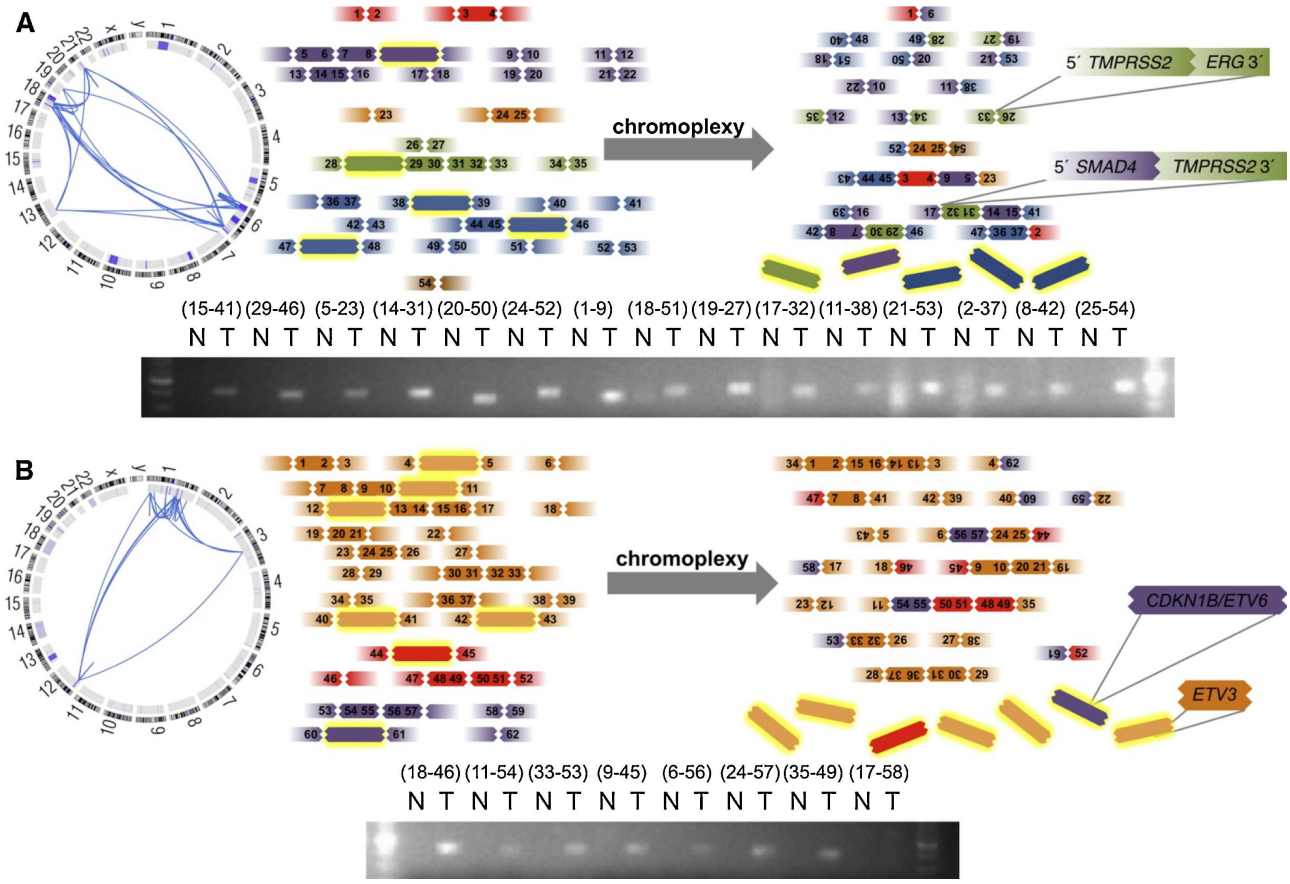


Fig. 4. Oncogene Driver Formation.
Chromothriptic Formation of Oncogenes. Figure 5 from Baca S.C., Prandi D., Lawrence M.S., Mosquera J.M., Romanel A., Drier Y., Park K., Kitayabashi N., MacDonal T.Y., Ghandi M., Van Allen E. "Puncutated Evolution of Prostate Cancer Genomes" (2013) Cell 153 (3) 666–677. Re-used by permission.

growth arrest in tissues [46,47], be linked with gross chromosomal morphological abnormalities (breaks, chains, rings, deletions, inversions, double minutes [21,40,42,45,48–53]), induce chromosomal translocations [42,43,45,48,53], cause multiple pronuclear divisions in anaphase as opposed to the normal bi-pronuclear separation, be linked with anaphase chromatin bridge formation [25,40,44], aneuploidy [43,44,54], errors of chromosomal segregation [25,44], and abnormalities of nuclear morphology [25,44,45,53,55]. Heritable ring and chain translocations and aneuploidy in germ cells has also been shown [43,51]. Major chromosomal aberrations and micronuclei have been shown in diverse tissues in humans including circulating lymphocytes in cannabis users [43], lymphocytes stimulated *in vitro* [40,54], polychromatic erythrocytes [43,45], bone marrow cells [41,43,45], lung cells [21,52] and human sperm [43,55]. Interestingly a UCLA group reported field cancerization and a super-multiplicative interaction between cannabis exposure and chromosomal breaks in a bleomycin-induced stimulated circulating lymphocyte clastogenic

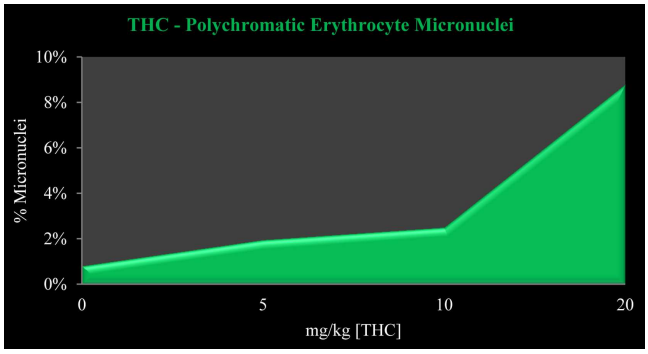


Fig. 5. Comparative Non-Linear Dose-Response Kinetics of THC and Thalidomide. Data from Table 2, Single day exposure, Zimmerman A.M. and Raj Y. 1980, "Influence of Cannabinoinds on Somatic Cells in vivo", Pharmacology 21 (4): 277–287.

assay in a case-control study of head and neck cancer [56]. Furthermore THC concentrations of 20 μM reduced the other key component of the intracellular cytoskeleton actin mRNA levels by 40%, and interactions between the centriole and the sub-cortical actin cloud has recently been shown to play a key role in the correct orientation of the centrosomes during mitosis [57].

4. Non-linear dose-response kinetics

One important observation to emerge from these studies is the non-linear dose response kinetics of cannabis in mutagenicity and genotoxicity studies (Fig. 5). Low dose THC and other cannabinoids have been found both in vitro (<5 μg/ml or <5 μmol/l) and in clinical studies (<1 joint/day) to be rarely associated with genotoxically mediated adverse outcomes [36,37,40–42,44,47–49,58–61]. Serum levels of 1 mmol/l have been reported after recreational use [62].

5. Cannabis cancerogenesis

Importantly cannabis use has also been positively associated in epidemiological studies with several cancers including aerodigestive cancers (head and neck [56], larynx, lung [63–65]), leukaemia, brain [66], prostate [67], cervix, testes [68] and bladder cancer [69–71]. Parental cannabis exposure during pregnancy has also been associated with the emergence of rhabdomyosarcoma [70], neuroblastoma [72] and acute myeloid leukaemia [73,74] in their young children (<5 years). The relative risk of such tumours is usually found to be 2–6 fold increased. Importantly these cannabis-related tumours in adults are often said to occur at much younger ages than those seen in non-users, and to be more highly aggressive [75,76]. In several cases a dose related response has been shown [56,65,68,71,73,77], which, together with a now plausible biological mechanism, implies causality. The present explication of the mechanics of chromothripsis, presumably occurring during in utero development, now provides a mechanism to account for such diverse and repeated findings. These mechanisms exist in addition to the mutagenic and free radical content of cannabis smoke [52,78,79] and its ability to activate pre-carcinogens [21,70,78,80].

It should be noted that not all such studies of mutagenesis in cannabis exposed individuals have been positive. Such diversity of outcomes relates to both in vitro and in vivo preclinical and clinical studies. One major limitation of many studies performed in western nations is the very limited cannabis exposure described amongst individuals in these reports. Indeed in one report "heavy cannabis use" was defined as more than 0.89 joints per day, and in another a lifetime exposure of more than 30 joint years (one joint per day for 30 years) was said to be heavy [80]. Conversely, studies from the developing world have quantitatively much greater cannabis exposures, and generally report a positive association.

One widely quoted negative study of cannabis carcinogenesis from California compared cancer cases and controls matched for age, sex and region [80]. In both groups the cannabis exposure was similar. Whilst this is a carefully matched design, the apparently serendipitous matching of cannabis exposure implied that it was not able to address the central research question relating to altered cancer outcomes of exposed and non-exposed individuals. Its negative finding was therefore not surprising. Furthermore the statistical analytic method employed in the study systematically excluded subjects exposed to high doses of cannabis to minimize outlier effects. If one correctly understands the addictive nature of cannabis and the highly non-linear dose-response shown in numerous cellular and preclinical genotoxicity assays, it is these higher dose exposures which are of the greatest interest, and are also most likely to carry important statistical signals.

6. Cannabis teratogenicity

Cannabis has also been associated with foetal abnormalities in many studies including low birth weight, foetal growth restriction, preterm birth spontaneous miscarriage [46,51,59,60,81], microotia/anotia, microphthalmia/anophthalmia, spina bifida, meningomyelocoele, anencephaly, cardiac defects including in particular cardiac septal defects, gastroschisis and many others [46,82]. Phocomelia (short or truncated forelimbs) has also been shown in testing in a similar preclinical model (hamster) to that which revealed the teratogenicity of thalidomide [46]. Dose-related effects were found [46,60,81]. Whilst these defects appear disparate and diverse, they all bear in common an arrest of cell growth and cell migration at critical developmental stages, consistent with the inhibition of mitosis noted with cannabis by various mechanisms. It has been noted that the doses used in some of these preclinical studies were high being in the 50–300 mg/kg range [46]. Nevertheless it is usual practice to take dose-response effects up to maximum tolerated doses in teratogenicity studies; cannabis use is increasing substantially in many places; the strength of cannabis available has increased over 20-fold since the 1960s [83]; cannabinoids are lipid soluble and likely accumulate to high concentrations in many fat rich body tissues including cell membranes, myelinated neural tissues and gonads; and cannabinoids have a long terminal half life of excretion; so that elevated levels in preclinical studies are not necessarily of no clinical relevance. Moreover there is virtual identity between the lists of deformities described in preclinical studies [46] and those found in epidemiological studies of human infants [82].

Parental cannabinoid exposure has also been linked to impaired intellectual performance, concentration and executive function, and hyperactivity amongst human child and adolescent offspring exposed *in utero* [47,84–86].

7. Cannabis-related mitochondrial inhibition

THC has also been shown to inhibit mitochondria after both in vitro and in vivo exposure of lung cells, brain cells and sperm in part by increasing their expression of uncoupling protein 2 [61,85,87–91]. Cannabis pyrollysates (partially burnt products of the smoked plant) also increase oxidative stress on many tissues [52,58,78]. These findings are important for several reasons. Oxidative stress is one of the leading theories of the causes of ageing and mutagenesis [92–96]. Energy generation is important for cells to cope with oxidative stress. Therefore the induction of increased oxidative stress coupled with reduced energy production and increased electron leak and production of free radical species

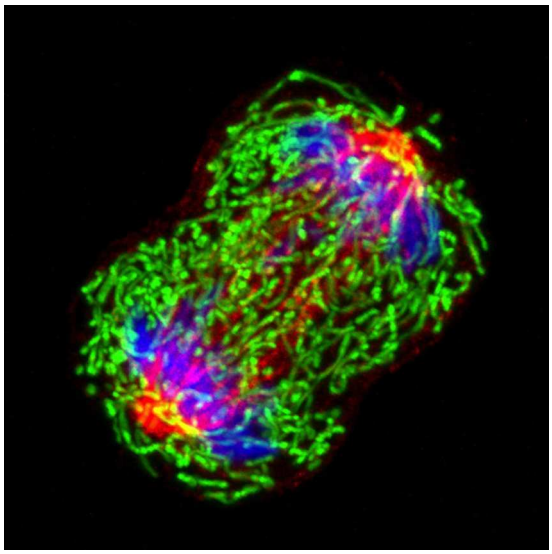


Fig. 6. Dividing Cell: Chromosomes, microtubules and mitochondria. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Dividing Cell; Tubulin in red; chromosomes in blue; mitochondria in green.
National Cancer Institute, University of Pittsburgh Cancer Institute,
Public Domain; https://visualsonline.cancer.gov/details.cfm?imageid=10708.

(and in many tissues reduced transcription of anti-oxidant defence proteins [78]) is a powerful double edged pro-ageing insult. Mitochondrial dysfunction is also one of the key hallmarks of cellular ageing [97–99]. This is also consistent with our own unpublished data employing radial arterial tonometry of cardiovascular stiffness (by previously described techniques [100]) of increased cardiovascular ageing (as a major surrogate for organismal aging) in cannabis exposed patients compared to both control non-smokers and tobacco-only smokers in both cross-sectional and longitudinal studies (unpublished data). This data in cannabis exposed patients is consistent with other reports of accelerated aging after tobacco and alcohol exposure [96] and after opioids [100–103].

8. Cannabis-related gametotoxicity, zygote toxicity and reproductive impairment

Moreover cell division, and DNA and chromosomal replication are very energy intensive processes. This point is well illustrated by Fig. 6 which stains the mitotic spindle, chromosomes and the dense network of mitochondria surrounding the mitotic apparatus at the end of anaphase. Perhaps unsurprisingly mitotic errors including chromosomal mis-segregation have been shown to be more common in older cells [99]. Importantly it has also been shown that improved energy production from aged oocyte mitochondria is associated with improved functional fidelity of the meiotic machinery and reduced errors of meiosis in female gametes and reduced subsequent conceptus loss [99]. Meiosis in ova is relatively error prone [17,99,104]. Cannabis has been shown to greatly increase the rate of zygote death after the first cell division by 50% [25]. The demonstration of sperm mitochondrial functional impairment [61] is similarly of great concern as it implies increased meiotic errors with the potential for transmission to subsequent generation/s. Cannabinoids have also been shown to importantly mediate several sperm specific critical genetic functions via CB1R including DNA nicking in preparation for tight packing, the re-packaging of DNA from histones to transitional proteins and then to protamines, and protection of packaged DNA [105,106]. Cannabinoids also play key functions in the reproductive tract, where they modify sperm activity, hypermotility and penetration, acrosome exocytosis and egg penetration [61,107–109]. Cannabinoids and CB1R are present at high concentration in the oviduct and Graafian follicle [61]. Exogenous cannabinoids have been shown to act as partial functional antagonists and disruptors of these natural yet critical endocannabinoid reactions [34,61,105,107].

9. Other microtubule functions

Microtubules are also essential to many other cell functions notably in stem cell niches and in neurons. It has been shown that the cell cycle, particularly in S and G2 phases, governs the human embryonic stem cell decision relating to the exit from pluripotency to cell differentiation (*via* a P53/ATM-ATR/CHEK2/CyclinB1/TGFβ/Nanog spindle checkpoint pathway) [110], and that microtubule structures (nanotubes) mediate the spreading of deterministic molecular signals (bone morphogenetic protein ligand decapentaplegic) from germ line niche cells to neighbouring stem cells (where it binds to its receptor Thickveins) and thus limit the stem cell maintenance signal to germ stem cells with which the hub support cells are in immediate contact [111]. Neuronal axons contain long microtubule bundles which can be up to one meter in length. Axons rapidly transport nutrients and proteins along using dynein and kinesin microtubule-based motors at speeds of up to 1 μm/s [15]. Hence THC based disruption of microtubular function has been associated with loss of axonal direction finding and an increase in target location errors, and errors of axonal sprouting [34,37].

The enzymes which metabolize cannabinoids in the brain (diacyl glyceryl lipase-α and monoacyl glyceryl lipase) and the distribution of CB1R change dramatically during in utero and early post-natal development with important implications for axonal pathfinding and thus corticofugal tract definition, and this process is disrupted by exogenous cannabinoids [47]. As in sperm development, the endocannabinoid system plays a key role in such major brain developmental processes as cell proliferation, neurogenesis, migration and axon pathfinding *via* CB1R, CB2R, TRPV1R, GPR55 and PPARα signalling and exophytocannabinoids act as partial antagonists and functional disruptors of this finely tuned system [47]. Hippocampal volume was found to be reduced in young adolescents following in utero exposure to cannabis, as have lasting alterations in glutamate, GABA, opioid serotonin and cholinergic muscarinic and nicotinic brain signalling [47,112].

These effects of cannabinoids explain the confusing and paradoxical effects of cannabis in cancer. Various cannabinoids have been proposed to have possible therapeutic effects on tumours and tumour growth in part by inhibition of DNA synthesis [43,50,113–116] but, as noted above, cannabinoids have also been linked epidemiologically with carcinogenesis. The effects of cannabis on tubulin and its association with cell growth inhibition explain these paradoxes – both can be true. Both cell cycle inhibition and arrest of cell growth, and occasional mutant cell escape via chromothriptic malignant induction can occur, both related to cannabis – tubulin interactions and in a dose dependent manner. Interestingly the function of the critical SAC checkpoint has been shown to be reduced in tetraploid cells due to TP53 suppression, so such environments may make both error prone chromosomal replication, and escape from the normal cell cycle controls, more common [7].

10. Other addictions

Interestingly similar comments can be made about several other addictions. Dependency syndromes associated with alcohol, tobacco, opioids and benzodiazepines have been associated with tumourigenesis [117–123]. Dependency on alcohol, benzo-

diazepines, opioids, cocaine and amphetamine has been linked with adverse morphological and developmental outcomes in children exposed in utero. Most chemical addictions are associated with foetal growth restriction [47,84,124] and many are associated with neurological or intellectual impairment in children exposed in utero [125]. Importantly opioids [126,127], alcohol [128,129], amphetamine [130], nicotine [131,132] and cocaine [133] have been shown to interact with tubulin polymerization and/or microtubule associated proteins. Indeed interference with tubulin dynamics now provides a mechanism whereby environmental agents do not need to be directly mutagenic to DNA bases or clastogenic to chromosomes themselves, but can nonetheless have a devastating effect on the integrity of the genetic information by interfering with the cellular machinery of meiosis in gametes [43,104,134,135]. Indeed all addictive drugs have been shown to interfere with mitosis [136] and to be genotoxic [137].

11. Epigenetic contributions to mutagenicity

It will also be noted that the discussion to this point has not considered the epigenetic revolution which is rapidly overtaking medicine. The origins of the Barker hypothesis of the foetal origins of adult disease has been attributed to the observation of the increased incidence of cardiovascular disease in children born to women exposed to the post-war famine in England [138,139]. Since that time many environmental agents have been linked with epigenetic change including alcohol [140–142], cocaine [143–148], amphetamine [149–152], opioids [153–156] and cannabinoids [41,59,157,158]. Indeed epigenomic changes have also been described with behavioural addictions such as gambling [159], and with stress exposure [160–164] which is a major common factor shared amongst all addictive syndromes. Whilst some epigenetic changes have been shown to be reversible in the short term [163], others have been shown to be passed on to offspring for three to four subsequent generations [165–167] via epigenetic modifications in oocytes and sperm [153,167–169]. Transgenerational transmission of epigenetic change through altered sperm DNA methylation has also been shown for cannabinoids in rats [157,170,171] and humans [172–174]. The well known immunmodulatory actions of cannabinoids also impact brain structure at sensitive developmental stages [62,175,176] and may be transferred to offspring epigenetically [62]. Since cannabinoids have long been known to selectively suppress nuclear histone mRNA and protein expression [43,50,177,178], alter the RNA transcriptome [157,171,179] and modify DNA methylation in key brain reward areas [157,170] thereby modifying all the main epigenomic regulatory systems, it seems inevitable that we are on the threshold of an exciting time to learn more about heritable pathways to genotoxic disease. Epigenetic inheritance has also been linked with paediatric gliomagensis [180]. Normal developmental [181] and ageing changes [182,183], cellular lineage specification amongst different tissues [181], single cell memory formation [62,183–185] and complex disease origins have been attributed in large part to epigenetic changes [186].

12. Conclusion

As mentioned above high dose cannabis and THC test positive in many genotoxicity assays, albeit often with a highly non-linear threshold like effects above low doses. As long ago as 2004 it was said that 3–41% of all neonates born in various North American communities had been exposed to cannabis [172]. Since cannabis is addictive [187], is becoming more potent [77,83,86], quickly builds up in adipose tissues [62,82] and seems generally to becoming more widely available under fluid regulatory regimes [187,188], real concern must be expressed that the rising population level of cannabinoid exposure will increasingly intersect the toxic thresholds for major genotoxicity including chromosomal clastogenicity secondary to interference and premature aging of the mitotic apparatus. Under such a conceptualization, it would appear that the real boon of restrictive cannabis regimes [189] is not their supposed success in any drug war, but their confinement in the populations they protect, to a low dose exposure paradigm which limits incident and transgenerational teratogenicity, ageing, mental retardation and cancerogenicity.

Conflict interests

The authors have no competing financial interests to declare.

Funding

This study received no external funding.

References

[1] C.Z. Zhang, A. Spektor, H. Cornils, J.M. Francis, E.K. Jackson, S. Liu, M. Meyerson, D. Pellman, Chromothripsis from DNA damage in micronuclei, Nature 522 (2015) 179–184.
[2] H. Kato, A.A. Sandberg, Chromosome pulverization in human binucleate cells following colcemid treatment, J. Cell Biol. 34 (1967) 35–45.
[3] K. Crasta, N.J. Ganem, R. Dagher, A.B. Lantermann, E.V. Ivanova, Y. Pan, L. Nezi, A. Protopopov, D. Chowdhury, D. Pellman, DNA breaks and chromosome pulverization from errors in mitosis, Nature 482 (2012) 53–58.
[4] J.V. Forment, A. Kaidi, S.P. Jackson, Chromothripsis and cancer: causes and consequences of chromosome shattering, Nat. Rev. Cancer 12 (2012) 663–670.
[5] S.C. Baca, D. Prandi, M.S. Lawrence, J.M. Mosquera, A. Romanel, Y. Drier, K. Park, N. Kitabayashi, T.Y. MacDonald, M. Ghandi, E. Van Allen, G.V. Kryukov, A. Sboner, J.P. Theurillat, T.D. Soong, E. Nickerson, D. Auclair, A. Tewari, H. Beltran, R.C. Onofrio, G. Boysen, C. Guiducci, C.E. Barbieri, K. Cibulskis, A. Sivachenko, S.L. Carter, G. Saksena, D. Voet, A.H. Ramos, W. Winckler, M. Cipicchio, K. Ardlie, P.W. Kantoff, M.F. Berger, S.B. Gabriel, T.R. Golub, M. Meyerson, E.S. Lander, O. Elemento, G. Getz, F. Demichelis, M.A. Rubin, L.A. Garraway, Punctuated evolution of prostate cancer genomes, Cell 153 (2013) 666–677.
[6] P.J. Hahn, Molecular biology of double-minute chromosomes, Bioessays 15 (1993) 477–484.
[7] A.Y. Kuznetsova, K. Seget, G.K. Moeller, M.S. de Pagter, J.A. de Roos, M. Durrbaum, C. Kuffer, S. Muller, G.J. Zaman, W.P. Kloosterman, Z. Storchova, Chromosomal instability, tolerance of mitotic errors and multidrug resistance are promoted by tetraploidization in human cells, Cell Cycle 14 (2015) 2810–2820.
[8] H.Y. Kroes, G.R. Monroe, B. van der Zwaag, K.J. Duran, C.G. de Kovel, M.J. van Roosmalen, M. Harakalova, I.J. Nijman, W.P. Kloosterman, R.H. Giles, N.V. Knoers, G. van Haaften, Joubert syndrome: genotyping a Northern European patient cohort, Eur. J. Hum. Genet. 24 (2016) 214–220.
[9] R.N. Tan, R.S. Witlox, Y. Hilhorst-Hofstee, C.M. Peeters-Scholte, N.S. den Hollander, C.A. Ruivenkamp, M.J. Hoffer, K.B. Hansson, M.J. van Roosmalen, W.P. Kloosterman, G.W. Santen, Clinical and molecular characterization of an infant with a tandem duplication and deletion of 19p13, Am. J. Med. Genet. A 167 (2015) 1884–1889.
[10] M.S. de Pagter, M.J. van Roosmalen, A.F. Baas, I. Renkens, K.J. Duran, E. van Binsbergen, M. Tavakoli-Yaraki, R. Hochstenbach, L.T. van der Veken, E. Cuppen, W.P. Kloosterman, Chromothripsis in healthy individuals affects multiple protein-coding genes and can result in severe congenital abnormalities in offspring, Am. J. Hum Genet. 96 (2015) 651–656.
[11] W.P. Kloosterman, V. Guryev, M. van Roosmalen, K.J. Duran, E. de Bruijn, S.C. Bakker, T. Letteboer, B. van Nesselrooij, R. Hochstenbach, M. Poot, E. Cuppen, Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline, Hum. Mol. Genet. 20 (2011) 1916–1924.
[12] C.Z. Zhang, M.L. Leibowitz, D. Pellman, Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements, Genes Dev. 27 (2013) 2513–2530.
[13] W.P. Kloosterman, M. Tavakoli-Yaraki, M.J. van Roosmalen, E. van Binsbergen, I. Renkens, K. Duran, L. Ballarati, S. Vergult, D. Giardino, K. Hansson, C.A. Ruivenkamp, M. Jager, A. van Haeringen, E.F. Ippel, T. Haaf, E. Passarge, R. Hochstenbach, B. Menten, L. Larizza, V. Guryev, M. Poot, E. Cuppen, Constitutional chromothripsis rearrangements involve clustered double-stranded DNA breaks and nonhomologous repair mechanisms, Cell Rep. 1 (2012) 648–655.
[14] W.P. Kloosterman, E. Cuppen, Chromothripsis in congenital disorders and cancer: similarities and differences, Curr. Opin. Cell Biol. 25 (2013) 341–348.

[15] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, Molecular Biology of the Cell, 1601, Garland Science, New York, 2008.
[16] S. Ruchaud, M. Carmena, W.C. Earnshaw, Chromosomal passengers: conducting cell division, Nat. Rev. Mol. Cell Biol. 8 (2007) 798–812.
[17] A.Z. Balboula, P. Stein, R.M. Schultz, K. Schindler, Knockdown of RBBP7 unveils a requirement of histone deacetylation for CPC function in mouse oocytes, Cell Cycle 13 (2014) 600–611.
[18] S. Lapenna, A. Giordano, Cell cycle kinases as therapeutic targets for cancer, Nat. Rev. 8 (2009) 547–566.
[19] L. Jia, S. Kim, H. Yu, Tracking spindle checkpoint signals from kinetochores to APC/C, Trends Biochem. Sci. 38 (2013) 302–311.
[20] A.W. Wyatt, C.C. Collins, In brief: chromothripsis and cancer, J. Pathol. 231 (2013) 1–3.
[21] R.M. Maertens, P.A. White, W. Rickert, G. Levasseur, G.R. Douglas, P.V. Bellier, J.P. McNamee, V. Thuppal, M. Walker, S. Desjardins, The genotoxicity of mainstream and sidestream marijuana and tobacco smoke condensates, Chem. Res. Toxicol. 22 (2009) 1406–1414.
[22] M.J. Jones, P.V. Jallepalli, Chromothripsis: chromosomes in crisis, Dev. Cell 23 (2012) 908–917.
[23] N.J. Ganem, D. Pellman, Linking abnormal mitosis to the acquisition of DNA damage, J. Cell Biol. 199 (2012) 871–881.
[24] G. Liu, J.B. Stevens, S.D. Horne, B.Y. Abdallah, K.J. Ye, S.W. Bremer, C.J. Ye, D.J. Chen, H.H. Heng, Genome chaos: survival strategy during crisis, Cell Cycle 13 (2014) 528–537.
[25] A. Morishima, Effects of cannabis and natural cannabinoids on chromosomes and ova, NIDA Res. Monogr. 44 (1984) 25–45.
[26] P.J. Stephens, C.D. Greenman, B. Fu, F. Yang, G.R. Bignell, L.J. Mudie, E.D. Pleasance, K.W. Lau, D. Beare, L.A. Stebbings, S. McLaren, M.L. Lin, D.J. McBride, I. Varela, S. Nik-Zainal, C. Leroy, M. Jia, A. Menzies, A.P. Butler, J.W. Teague, M.A. Quail, J. Burton, H. Swerdlow, N.P. Carter, L.A. Morsberger, C. Iacobuzio-Donahue, G.A. Follows, A.R. Green, A.M. Flanagan, M.R. Stratton, P.A. Futreal, P.J. Campbell, Massive genomic rearrangement acquired in a single catastrophic event during cancer development, Cell 144 (2011) 27–40.
[27] J.J. Molenaar, J. Koster, D.A. Zwijnenburg, P. van Sluis, L.J. Valentijn, I. van der Ploeg, M. Hamdi, J. van Nes, B.A. Westerman, J. van Arkel, M.E. Ebus, F. Haneveld, A. Lakeman, L. Schild, P. Molenaar, P. Stroeken, M.M. van Noesel, I. Ora, E.E. Santo, H.N. Caron, E.M. Westerhout, R. Versteeg, Sequencing of neuroblastoma identifies chromothripsis and defects in neuritogenesis genes, Nature 483 (2012) 589–593.
[28] J.M. Furgason, R.F. Koncar, S.K. Michelhaugh, F.H. Sarkar, S. Mittal, A.E. Sloan, J.S. Barnholtz-Sloan, M. Bahassi el, Whole genome sequence analysis links chromothripsis to EGFR, MDM2, MDM4, and CDK4 amplification in glioblastoma, Oncoscience 2 (2015) 618–628.
[29] W.P. Kloosterman, M. Hoogstraat, O. Paling, M. Tavakoli-Yaraki, I. Renkens, J.S. Vermaat, M.J. van Roosmalen, S. van Lieshout, I.J. Nijman, W. Roessingh, R. van 't Slot, J. van de Belt, V. Guryev, M. Koudijs, E. Voest, E. Cuppen, Chromothripsis is a common mechanism driving genomic rearrangements in primary and metastatic colorectal cancer, Genome Biol. 12 (2011) R103.
[30] W.P. Kloosterman, J. Koster, J.J. Molenaar, Prevalence and clinical implications of chromothripsis in cancer genomes, Curr. Opin. Oncol. 26 (2014) 64–72.
[31] D.H. McDermott, J.L. Gao, Q. Liu, M. Siwicki, C. Martens, P. Jacobs, D. Velez, E. Yim, C.R. Bryke, N. Hsu, Z. Dai, M.M. Marquesen, E. Stregevsky, N. Kwatemaa, N. Theobald, D.A. Long Priel, S. Pittaluga, M.A. Raffeld, K.R. Calvo, I. Maric, R. Desmond, K.L. Holmes, D.B. Kuhns, K. Balabanian, F. Bachelerie, S.F. Porcella, H.L. Malech, P.M. Murphy, Chromothriptic cure of WHIM syndrome, Cell 160 (2015) 686–699.
[32] R. Sotillo, E. Hernando, E. Diaz-Rodriguez, J. Teruya-Feldstein, C. Cordon-Cardo, S.W. Lowe, R. Benezra, Mad2 overexpression promotes aneuploidy and tumorigenesis in mice, Cancer Cell 11 (2007) 9–23.
[33] R.M. Ricke, K.B. Jeganathan, J.M. van Deursen, Bub1 overexpression induces aneuploidy and tumor formation through Aurora B kinase hyperactivation, J. Cell Biol. 193 (2011) 1049–1064.
[34] G. Tortoriello, C.V. Morris, A. Alpar, J. Fuzik, S.L. Shirran, D. Calvigioni, E. Keimpema, C.H. Botting, K. Reinecke, T. Herdegen, M. Courtney, Y.L. Hurd, T. Harkany, Miswiring the brain: delta9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway, EMBO J. 33 (2014) 668–685.
[35] S.L. Palmer, P.G. Meyehof, A.M. Zimmerman, Effects of delta-tetrahydrocannabinol on some aspects of mitotic organization, J. Cell Biol. 91 (1981) 319a.
[36] S.K. Tahir, A.M. Zimmerman, Influence of marihuana on cellular structures and biochemical activities, Pharmacol. Biochem. Behav. 40 (1991) 617–623.
[37] S.K. Tahir, J.E. Trogadis, J.K. Stevens, A.M. Zimmerman, Cytoskeletal organization following cannabinoid treatment in undifferentiated and differentiated PC12 cells, Biochem. Cell Biol. 70 (1992) 1159–1173.
[38] R.G. Wilson Jr., S.K. Tahir, R. Mechoulam, S. Zimmerman, A.M. Zimmerman, Cannabinoid enantiomer action on the cytoarchitecture, Cell Biol. Int. 20 (1996) 147–157.
[39] S.J. Parker, B.S. Zuckerman, A.M. Zimmermann, The effects of maternal marijuana use during pregnancy on fetal growth, in: G.G. Nahas, K.M. Sutin, D.J. Harvey, S. Agurell (Eds.), Marijuana in Medicine, Humana PressTotowa, New York, 1999, pp. 461–468.
[40] V.J. Koller, F. Ferk, H. Al-Serori, M. Misik, A. Nersesyan, V. Auwarter, T. Grummt, S. Knasmuller, Genotoxic properties of representatives of alkylindazoles and aminoalkyl-indoles which are consumed as synthetic cannabinoids, Food Chem. Toxicol. 80 (2015) 130–136.
[41] V.J. Koller, V. Auwarter, T. Grummt, B. Moosmann, M. Misik, S. Knasmuller, Investigation of the in vitro toxicological properties of the synthetic cannabimimetic drug CP-47,497-C8, Toxicol. Appl. Pharmacol. 277 (2014) 164–171.
[42] A.M. Zimmerman, A.Y. Raj, Influence of cannabinoids on somatic cells in vivo, Pharmacology 21 (1980) 277–287.
[43] S. Zimmerman, A.M. Zimmerman, Genetic effects of marijuana, Int. J. Addict. 25 (1990) 19–33.
[44] R.T. Henrich, T. Nogawa, A. Morishima, In vitro induction of segregational errors of chromosomes by natural cannabinoids in normal human lymphocytes, Environ. Mutagen. 2 (1980) 139–147.
[45] A.M. Zimmerman, S. Zimmerman, Cytogenetic studies of cannabinoid effects, in: M.C. Braude, A.M. Zimmerman (Eds.), Genetic and Perinatal Effects of Abused Substances, Academic Press Inc., Harcourt, Brace Jovanovich, New York, 1987, pp. 95–112.
[46] W.F. Geber, L.C. Schramm, Teratogenicity of marihuana extract as influenced by plant origin and seasonal variation, Arch. Int. Pharmacodyn. Ther. 177 (1969) 224–230.
[47] C.S. Wu, C.P. Jew, H.C. Lu, Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain, Future Neurol. 6 (2011) 459–480.
[48] D.G. Gilmour, A.D. Bloom, K.P. Lele, E.S. Robbins, C. Maximilian, Chromosomal aberrations in users of psychoactive drugs, Arch. Gen. Psychiatry 24 (1971) 268–272.
[49] M.A. Stenchever, T.J. Kunysz, M.A. Allen, Chromosome breakage in users of marihuana, Am. J. Obstet. Gynecol. 118 (1974) 106–113.
[50] M.J. Mon, R.L. Jansing, S. Doggett, J.L. Stein, G.S. Stein, Influence of delta9-tetrahydrocannabinol on cell proliferation and macromolecular biosynthesis in human cells, Biochem. Pharmacol. 27 (1978) 1759–1765.
[51] S. Dalterio, F. Badr, A. Bartke, D. Mayfield, Cannabinoids in male mice: effects on fertility and spermatogenesis, Science 216 (1982) 315–316.
[52] H.R. Kim, B.H. Son, S.Y. Lee, K.H. Chung, S.M. Oh, The role of p53 in marijuana smoke condensates-induced genotoxicity and apoptosis, Environ. Health Toxicol. 27 (2012) e2012017.
[53] A.M. Zimmerman, S. Zimmerman, A.Y. Raj, Effects of cannabinoids on spermatogensis in mice, in: G.G. Nahas, K.M. Sutin, D.J. Harvey, S. Agurell (Eds.), Marijuana and Medicine, Humana Press Totowa, New York, 1999, pp. 347–358.
[54] A. Morishima, R.T. Henrich, J. Jayaraman, G.G. Nahas, Hypoploid metaphases in cultured lymphocytes of marihuana smokers, Adv. Biosci. 22–23 (1978) 371–376.
[55] W.C. Hembree Jr., G.G. Nahas, P. Zeidenberg, H.F.S. Huang, Changes in Human Spermatozoa Associated with High Dose Marijuana Smoking, in: G.G. Nahas, K.M. Sutin, D.J. Harvey, S. Agurell (Eds.), Humana Press Totowa, New York, 1999, pp. 367–378.
[56] Z.F. Zhang, H. Morgenstern, M.R. Spitz, D.P. Tashkin, G.P. Yu, J.R. Marshall, T.C. Hsu, S.P. Schantz, Marijuana use and increased risk of squamous cell carcinoma of the head and neck, Cancer Epidemiol. Biomarkers Prev. 8 (1999) 1071–1078.
[57] M. Kwon, M. Bagonis, G. Danuser, D. Pellman, Direct microtubule-binding by myosin-10 orients centrosomes toward retraction fibers and subcortical actin clouds, Dev. Cell 34 (2015) 323–337.
[58] T. Sarafian, N. Habib, J.T. Mao, I.H. Tsu, M.L. Yamamoto, E. Hsu, D.P. Tashkin, M.D. Roth, Gene expression changes in human small airway epithelial cells exposed to Delta9-tetrahydrocannabinol, Toxicol. Lett. 158 (2005) 95–107.
[59] M. Khare, A.H. Taylor, J.C. Konje, S.C. Bell, Delta9-tetrahydrocannabinol inhibits cytotrophoblast cell proliferation and modulates gene transcription, Mol. Hum. Reprod. 12 (2006) 321–333.
[60] J.D.P. Graham, Cannabis and health, in: J.D.P. Graham (Ed.), Cannabis and Health, Academic PressLondon, New York, San Francisco, 1976, pp. 271–320.
[61] M. Rossato, F. Ion Popa, M. Ferigo, G. Clari, C. Foresta, Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function, J. Clin. Endocrinol. Metab. 90 (2005) 984–991.
[62] C. Lombard, V.L. Hegde, M. Nagarkatti, P.S. Nagarkatti, Perinatal exposure to Delta9-tetrahydrocannabinol triggers profound defects in T cell differentiation and function in fetal and postnatal stages of life, including decreased responsiveness to HIV antigens, J. Pharmacol. Exp. Ther. 339 (2011) 607–617.
[63] S. Aldington, M. Harwood, B. Cox, M. Weatherall, L. Beckert, A. Hansell, A. Pritchard, G. Robinson, R. Beasley, Cannabis use and risk of lung cancer: a case-control study, Eur. Respir. J. 31 (2008) 280–286.
[64] N. Voirin, J. Berthiller, V. Benhaim-Luzon, M. Boniol, K. Straif, W.B. Ayoub, F.B. Ayed, A.J. Sasco, Risk of lung cancer and past use of cannabis in Tunisia, J. Thorac. Oncol. 1 (2006) 577–579.
[65] J. Berthiller, K. Straif, M. Boniol, N. Voirin, V. Benhaim-Luzon, W.B. Ayoub, I. Dari, S. Laouamri, M. Hamdi-Cherif, M. Bartal, F.B. Ayed, A.J. Sasco, Cannabis smoking and risk of lung cancer in men: a pooled analysis of three studies in Maghreb, J. Thorac. Oncol. 3 (2008) 1398–1403.
[66] J.T. Efird, G.D. Friedman, S. Sidney, A. Klatsky, L.A. Habel, N.V. Udaltsova, S. Van den Eeden, L.M. Nelson, The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors, J. Neuro-Oncology. 68 (2004) 57–69.

[67] S. Sidney, C.P. Quesenberry Jr., G.D. Friedman, I.S. Tekawa, Marijuana use and cancer incidence (California, United States), Cancer Causes Control 8 (1997) 722–728.
[68] J.R. Daling, D.R. Doody, X. Sun, B.L. Trabert, N.S. Weiss, C. Chen, M.L. Biggs, J.R. Starr, S.K. Dey, S.M. Schwartz, Association of marijuana use and the incidence of testicular germ cell tumors, Cancer 115 (2009) 1215–1223.
[69] A.S. Reece, Chronic toxicology of cannabis, Clin. Toxicol. (2009) ()in press.
[70] M. Hashibe, K. Straif, D.P. Tashkin, H. Morgenstern, S. Greenland, Z.F. Zhang, Epidemiologic review of marijuana use and cancer risk, Alcohol (Fayetteville N.Y) 35 (2005) 265–275.
[71] J.A. Chacko, J.G. Heiner, W. Siu, M. Macy, M.K. Terris, Association between marijuana use and transitional cell carcinoma, Urology 67 (2006) 100–104.
[72] E.C. Bluhm, J. Daniels, B.H. Pollock, A.F. Olshan, Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States), Cancer Causes Control 17 (2006) 663–669.
[73] L.L. Robison, J.D. Buckley, A.E. Daigle, R. Wells, D. Benjamin, D.C. Arthur, G.D. Hammond, Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group), Cancer 63 (1989) 1904–1911.
[74] W.Q. Wen, X.O. Shu, M. Steinbuch, R.K. Severson, G.H. Reaman, J.D. Buckley, L.L. Robison, Paternal military service and risk for childhood leukemia in offspring, Am. J. Epidemiol. 151 (2000) 231–240.
[75] S. Bhattacharyya, S. Mandal, S. Banerjee, G.K. Mandal, A.K. Bhowmick, N. Murmu, Cannabis smoke can be a major risk factor for early-age laryngeal cancer-a molecular signaling-based approach, Tumour. Biol. 36 (2015) 6029–6036.
[76] M. Hashibe, D.E. Ford, Z.F. Zhang, Marijuana smoking and head and neck cancer, J. Clin. Pharmacol. 42 (2002) 103S–107S.
[77] W. Hall, The adverse health effects of cannabis use: what are they, and what are their implications for policy? Int. J. Drug Policy 20 (2009) 458–466.
[78] R.M. Maertens, P.A. White, A. Williams, C.L. Yauk, A global toxicogenomic analysis investigating the mechanistic differences between tobacco and marijuana smoke condensates in vitro, Toxicology 308 (2013) 60–73.
[79] F.W. Busch, D.A. Seid, E.T. Wei, Mutagenic activity of marihuana smoke condensates, Cancer Lett. 6 (1979) 319–324.
[80] M. Hashibe, H. Morgenstern, Y. Cui, D.P. Tashkin, Z.F. Zhang, W. Cozen, T.M. Mack, S. Greenland, Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study, Cancer Epidemiol. Biomarkers Prev. 15 (2006) 1829–1834.
[81] W.F. Geber, L.C. Schramm, Effect of marihuana extract on fetal hamsters and rabbits, Toxicol. Appl. Pharmacol. 14 (1969) 276–282.
[82] M.B. Forrester, R.D. Merz, Risk of selected birth defects with prenatal illicit drug use Hawaii, 1986–2002, J. Toxicol. Environ. Health 70 (2007) 7–18.
[83] W. Hall, L. Degenhardt, High potency cannabis: a risk factor for dependence, poor psychosocial outcomes, and psychosis, BMJ (Clinical research ed) 350 (2015) h1205.
[84] N. Nora Volkow (Director, George Koob (Director, NIAAA), Alan Guttmacher (Director, NICHD), Bob Croyle (Director, Divison of Cancer Control and Population Sciences, NCI), National Longitudinal Study of the Neurodevelopmental Consequences of Substance Use, National Institutes of Health, Bethseda, Maryland, (2014).
[85] Adverse Health Effects of Marijuana Use, New England Journal of Medicine, 371 (2014) 878–879.
[86] N.D. Volkow, R.D. Baler, W.M. Compton, S.R.B. Weiss, Adverse health effects of marijuana use, N. Engl. J. Med. 370 (2014) 2219–2227.
[87] T.A. Sarafian, S. Kouyoumjian, F. Khoshaghideh, D.P. Tashkin, M.D. Roth, Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics, Am. J. Physiol. 284 (2003) L298–306.
[88] T.A. Sarafian, N. Habib, M. Oldham, N. Seeram, R.P. Lee, L. Lin, D.P. Tashkin, M.D. Roth, Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo, Am. J. Physiol. 290 (2006) L1202–1209.
[89] V. Wolff, O. Rouyer, A. Schlagowski, J. Zoll, J.S. Raul, C. Marescaux, Étude de l'effet du THC sur la respiration mitochondriale du cerveau de rat. Une piste de réflexion pour expliquer le lien entre la consommation de cannabis et la survenue d'infarctus cérébral chez l'homme Study of the effect of THC on mitochondrial respiration of the rat brain. One line of thought to explain the link between cannabis use and the occurrence of cerebral infarction in men Revue Neurologique, Neurol. Rev. 170 (2014) A19–A20.
[90] Z.S. Badawy, K.R. Chohan, D.A. Whyte, H.S. Penefsky, O.M. Brown, A.K. Souid, Cannabinoids inhibit the respiration of human sperm, Fertil. Steril. 91 (2009) 2471–2476.
[91] B. Costa, M. Colleoni, Changes in rat brain energetic metabolism after exposure to anandamide or Delta(9)-tetrahydrocannabinol, Eur. J. Pharmacol. 395 (2000) 1–7.
[92] C. Lopez-Otin, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The hallmarks of aging, Cell 153 (2013) 1194–1217.
[93] R.S. Balaban, S. Nemoto, T. Finkel, Mitochondria, oxidants, and aging, Cell 120 (2005) 483–495.
[94] E.C. Hadley, E.G. Lakatta, M. Morrison-Bogorad, H.R. Warner, R.J. Hodes, The future of aging therapies, Cell 120 (2005) 557–567.
[95] T.B. Kirkwood, Understanding the odd science of aging, Cell 120 (2005) 437–447.
[96] A.S. Fauci, E. Braunwald, D.L. Kapser, S.L. Hauser, D.L. Longo, J.L. Jameson, Harrison's Principles of Internal Medicine, 17th edition, McGraw Hill, New York, 2008, pp. 2754.
[97] Secrets for Staying Young, Cell, 161, 1235.
[98] P. Katajisto, J. Döhla, C.L. Chaffer, N. Pentinmikko, N. Marjanovic, S. Iqbal, R. Zoncu, W. Chen, R.A. Weinberg, D.M. Sabatini, Asymmetric apportioning of aged mitochondria between daughter cells is required for stemness, Science 348 (2015) 340–343.
[99] A. Ben-Meir, E. Burstein, A. Borrego-Alvarez, J. Chong, E. Wong, T. Yavorska, T. Naranian, M. Chi, Y. Wang, Y. Bentov, J. Alexis, J. Meriano, H.K. Sung, D.L. Gasser, K.H. Moley, S. Hekimi, R.F. Casper, A. Jurisicova, Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging, Aging Cell 14 (2015) 887–895.
[100] A.S. Reece, G.K. Hulse, impact of lifetime opioid exposure on arterial stiffness and vascular age: cross-sectional and longitudinal studies in men and women, BMJ Open 4 (2014) 1–19.
[101] A.S. Reece, G.K. Hulse, Impact of opioid pharmacotherapy on arterial stiffness and vascular ageing: cross-sectional and longitudinal studies, Cardiovasc. Toxicol. 13 (2013) 254–266.
[102] A.S. Reece, G.K. Hulse, Reduction in arterial stiffness and vascular age by naltrexone-Induced interruption of opiate agonism, Br. Med. J. – Open 3 (2013) (pii: e002610).
[103] G.L.F. Cheng, H. Zeng, M.K. Leung, H.J. Zhang, B.W.M. Lau, Y.P. Liu, G.X. Liu, P.C. Sham, C.C.H. Chan, K.F. So, T.M.C. Lee, Heroin abuse accelerates biological aging: a novel insight from telomerase and brain imaging interaction, Transl. Psychiatry 3 (2013) e260.
[104] S. Pfender, V. Kuznetsov, M. Pasternak, T. Tischer, B. Santhanam, M. Schuh, Live imaging RNAi screen reveals genes essential for meiosis in mammalian oocytes, Nature 524 (2015) 239–242.
[105] T. Chioccarelli, G. Cacciola, L. Altucci, S.E. Lewis, L. Simon, G. Ricci, C. Ledent, R. Meccariello, S. Fasano, R. Pierantoni, G. Cobellis, Cannabinoid receptor 1 influences chromatin remodeling in mouse spermatids by affecting content of transition protein 2 mRNA and histone displacement, Endocrinology 151 (2010) 5017–5029.
[106] G. Cacciola, T. Chioccarelli, L. Altucci, C. Ledent, J.I. Mason, S. Fasano, R. Pierantoni, G. Cobellis, Low 17beta-estradiol levels in CNR1 knock-out mice affect spermatid chromatin remodeling by interfering with chromatin reorganization, Biol. Reprod. 88 (2013) 152.
[107] S.E. Lewis, M. Maccarrone, Endocannabinoids, sperm biology and human fertility, Pharmacol. Res. 60 (2009) 126–131.
[108] N. Battista, C. Rapino, M. Di Tommaso, M. Bari, N. Pasquariello, M. Maccarrone, Regulation of male fertility by the endocannabinoid system, Mol. Cell. Endocrinol. 286 (2008) S17–23.
[109] M.R. Miller, N. Mannowetz, A.T. Iavarone, R. Safavi, E.O. Gracheva, J.F. Smith, R.Z. Hill, D.M. Bautista, Y. Kirichok, P.V. Lishko, Unconventional endocannabinoid signaling governs sperm activation via the sex hormone progesterone, Science 352 (2016) 555–559.
[110] K.A. Gonzales, H. Liang, Y.S. Lim, Y.S. Chan, J.C. Yeo, C.P. Tan, B. Gao, B. Le, Z.Y. Tan, K.Y. Low, Y.C. Liou, F. Bard, H.H. Ng, Deterministic restriction on pluripotent state dissolution by cell-Cycle pathways, Cell 162 (2015) 564–579.
[111] M. Inaba, M. Buszczak, Y.M. Yamashita, Nanotubes mediate niche-stem-cell signalling in the Drosophila testis, Nature 523 (2015) 329–332.
[112] S. Navakkode, M. Korte, Pharmacological activation of CB1 receptor modulates long term potentiation by interfering with protein synthesis, Neuropharmacology 79 (2014) 525–533.
[113] A.E. Munson, L.S. Harris, M.A. Friedman, W.L. Dewey, R.A. Carchman, Antineoplastic activity of cannabinoids, J. Natl. Cancer Inst. 55 (1975) 597–602.
[114] A. Preet, R.K. Ganju, J.E. Groopman, Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo, Oncogene 27 (2008) 339–346.
[115] R.A. Carchman, L.S. Harris, A.E. Munson, The inhibition of DNA synthesis by cannabinoids, Cancer Res. 36 (1976) 95–100.
[116] S.K. Tilak, A.M. Zimmerman, Effects of cannabinoids on macromolecular synthesis in isolated spermatogenic cells, Pharmacology 29 (1984) 343–350.
[117] E. Braunwald, A.S. Fauci, D.l Kasper., S.L. Hauser, D.L. Longo, J. J.L., Harrison's Principles of Internal Medicine, 15th Edition, McGraw Hill New York (2001), pp. 1–2630.
[118] D.F. Kripke, R.D. Langer, L.E. Kline, Hypnotics' association with mortality or cancer: a matched cohort study, BMJ Open 2 (2012) e000850.
[119] S. Behmard, A. Sadeghi, M.R. Mohareri, R. Kadivar, Positive association of opium addiction and cancer of the bladder. Results of urine cytology in 3,500 opium addicts, Acta Cytol. 25 (1981) 142–146.
[120] M.S. Fahmy, A. Sadeghi, S. Behmard, Epidemiologic study of oral cancer in Fars Province, Iran, Community Dent. Oral Epidemiol. 11 (1983) 50–58.
[121] A. Ghavamzadeh, A. Moussavi, M. Jahani, M. Rastegarpanah, M. Iravani, Esophageal cancer in Iran, Semin. Oncol. 28 (2001) 153–157.
[122] M.R. Mousavi, M.A. Damghani, A.A. Haghdoust, A. Khamesipour, Opium and risk of laryngeal cancer, Laryngoscope 113 (2003) 1939–1943.
[123] H. Khademi, R. Malekzadeh, A. Pourshams, E. Jafari, R. Salahi, S. Semnani, B. Abaie, F. Islami, S. Nasseri-Moghaddam, A. Etemadi, G. Byrnes, C.C. Abnet, S.M. Dawsey, N.E. Day, P.D. Pharoah, P. Boffetta, P. Brennan, F. Kamangar, Opium use and mortality in Golestan Cohort Study: prospective cohort study of 50 000 adults in Iran, BMJ (Clin. Res. ed.) 344 (2012) e2502.
[124] C. Davitian, M. Uzan, A. Tigaizin, G. Ducarme, H. Dauphin, C. Poncelet, [Maternal cannabis use and intra-uterine growth restriction], Gynecol. Obstet. Fertil. 34 (2006) 632–637.

[125] T.M. Pinkert, Current research on the consequences of maternal drug abuse, NIDA Res. Monogr. 1 (1985) 1–113.
[126] C. Marie-Claire, C. Courtin, B.P. Roques, F. Noble, Cytoskeletal genes regulation by chronic morphine treatment in rat striatum, Neuropsychopharmacology 29 (2004) 2208–2215.
[127] R.Y. Tsai, Y.C. Cheng, C.S. Wong, (+)-Naloxone inhibits morphine-induced chemotaxis via prevention of heat shock protein 90 cleavage in microglia, J. Formos Med. Assoc. 114 (2015) 446–455.
[128] A.M. Erdozain, B. Morentin, L. Bedford, E. King, D. Tooth, C. Brewer, D. Wayne, L. Johnson, H.K. Gerdes, P. Wigmore, L.F. Callado, W.G. Carter, Alcohol-related brain damage in humans, PLoS One 9 (2014) e93586.
[129] B.C. Feltes, J. de Faria Poloni, I.J. Nunes, D. Bonatto, Fetal alcohol syndrome, chemo-biology and OMICS: ethanol effects on vitamin metabolism during neurodevelopment as measured by systems biology analysis, OMICS 18 (2014) 344–363.
[130] S. Fernandes, S. Salta, T. Summavielle, Methamphetamine promotes alpha-tubulin deacetylation in endothelial cells: the protective role of acetyl-L-carnitine, Toxicol. Lett. 234 (2015) 131–138.
[131] M.D. Minana, C. Montoliu, M. Llansola, S. Grisolia, V. Felipo, Nicotine prevents glutamate-induced proteolysis of the microtubule-associated protein MAP-2 and glutamate neurotoxicity in primary cultures of cerebellar neurons, Neuropharmacology 37 (1998) 847–857.
[132] P. Poggi, M.T. Rota, R. Boratto, The volatile fraction of cigarette smoke induces alterations in the human gingival fibroblast cytoskeleton, J. Periodontal Res. 37 (2002) 230–235.
[133] T.A. de Freitas, R.P. Palazzo, F.M. de Andrade, C.L. Reichert, F. Pechansky, F. Kessler, C.B. de Farias, G.G. de Andrade, S. Leistner-Segal, S.W. Maluf, Genomic instability in human lymphocytes from male users of crack cocaine, Int. J. Environ. Res. Public Health 11 (2014) 10003–10015.
[134] J. Dean, Exacting requirements for development of the egg, N. Engl. J. Med. 374 (2016) 279–280.
[135] R. Feng, Q. Sang, Y. Kuang, X. Sun, Z. Yan, S. Zhang, J. Shi, G. Tian, A. Luchniak, Y. Fukuda, B. Li, M. Yu, J. Chen, Y. Xu, L. Guo, R. Qu, X. Wang, Z. Sun, M. Liu, H. Shi, H. Wang, Y. Feng, R. Shao, R. Chai, Q. Li, Q. Xing, R. Zhang, E. Nogales, L. Jin, L. He, M.L. Gupta, N.J. Cowan, L. Wang, Mutations in TUBB8 and human oocyte meiotic arrest, New Engl. J. Med. 374 (2016) 223–232.
[136] A.J. Eisch, Adult neurogenesis: implications for psychiatry, Prog. Brain Res. 138 (2002) 315–342.
[137] J.H. Li, L.F. Lin, Genetic toxicology of abused drugs: a brief review, Mutagenesis 13 (1998) 557–565.
[138] D.J. Barker, The fetal and infant origins of adult disease, B.M.J 301 (1990) 1111.
[139] D.J. Barker, Fetal origins of cardiovascular disease, Ann. Med. 31 (Suppl. 1) (1999) 3–6.
[140] T. Hillemacher, H. Frieling, T. Hartl, J. Wilhelm, J. Kornhuber, S. Bleich, Promoter specific methylation of the dopamine transporter gene is altered in alcohol dependence and associated with craving, J. Psychiatr. Res. 43 (2009) 388–392.
[141] S. Rahman, Epigenetic mechanisms: targets for treatment of alcohol dependence and drug addiction, CNS Neurol. Disord. Drug Targets 11 (2012) 101.
[142] I. Ponomarev, S. Wang, L. Zhang, R.A. Harris, R.D. Mayfield, Gene coexpression networks in human brain identify epigenetic modifications in alcohol dependence, J. Neurosci. 32 (2012) 1884–1897.
[143] F.M. Vassoler, S.L. White, H.D. Schmidt, G. Sadri-Vakili, R.C. Pierce, Epigenetic inheritance of a cocaine-resistance phenotype, Nat. Neurosci. 16 (2013) 42–47.
[144] W. Renthal, A. Kumar, G. Xiao, M. Wilkinson, H.E. Covington 3rd, I. Maze, D. Sikder, A.J. Robison, Q. LaPlant, D.M. Dietz, S.J. Russo, V. Vialou, S. Chakravarty, T.J. Kodadek, A. Stack, M. Kabbaj, E.J. Nestler, Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins, Neuron 62 (2009) 335–348.
[145] P.J. Kennedy, J. Feng, A.J. Robison, I. Maze, A. Badimon, E. Mouzon, D. Chaudhury, D.M. Damez-Werno, S.J. Haggarty, M.H. Han, R. Bassel-Duby, E.N. Olson, E.J. Nestler, Class I HDAC inhibition blocks cocaine-induced plasticity by targeted changes in histone methylation, Nat. Neurosci. 16 (2013) 434–440.
[146] H.E. Covington III., I. Maze, H. Sun, H.M. Bomze, K.D. DeMaio, E.Y. Wu, D.M. Dietz, M.K. Lobo, S. Ghose, E. Mouzon, R.L. Neve, C.A. Tamminga, E.J. Nestler, A role for repressive histone methylation in cocaine-Induced vulnerability to stress, Neuron 71 (2011) 656–670.
[147] F.F. Caputi, M. Di Benedetto, D. Carretta, S. Bastias del Carmen Candia, C. D'Addario, C. Cavina, S. Candeletti, P. Romualdi, Dynorphin/KOP and nociceptin/NOP gene expression and epigenetic changes by cocaine in rat striatum and nucleus accumbens, Prog. Neuropsychopharmacol. Biol. Psychiatry. 49 (2014) 36–46.
[148] Q. Zhao, J. Hou, B. Chen, X. Shao, R. Zhu, Q. Bu, H. Gu, Y. Li, B. Zhang, C. Du, D. Fu, J. Kong, L. Luo, H. Long, H. Li, Y. Deng, Y. Zhao, X. Cen, Prenatal cocaine exposure impairs cognitive function of progeny via insulin growth factor II epigenetic regulation, Neurobiol. Dis. 82 (2015) 54–65.
[149] A. Godino, S. Jayanthi, J.L. Cadet, Epigenetic landscape of amphetamine and methamphetamine addiction in rodents, Epigenetics 10 (2015) 574–580.
[150] X. Li, F.J. Rubio, T. Zeric, J.M. Bossert, S. Kambhampati, H.M. Cates, P.J. Kennedy, Q.R. Liu, R. Cimbro, B.T. Hope, E.J. Nestler, Y. Shaham, Incubation of methamphetamine craving is associated with selective increases in expression of Bdnf and trkb, glutamate receptors, and epigenetic enzymes in cue-activated fos-expressing dorsal striatal neurons, J. Neurosci. 35 (2015) 8232–8244.
[151] A. Aguilar-Valles, T. Vaissiere, E.M. Griggs, M.A. Mikaelsson, I.F. Takacs, E.J. Young, G. Rumbaugh, C.A. Miller, Methamphetamine-associated memory is regulated by a writer and an eraser of permissive histone methylation, Biol. Psychiatry 76 (2014) 57–65.
[152] A. Sadakierska-Chudy, M. Frankowska, M. Filip, Mitoepigenetics and drug addiction, Pharmacol. Ther. 144 (2014) 226–233.
[153] D. Govorko, R.A. Bekdash, C. Zhang, D.K. Sarkar, Male germline transmits fetal alcohol adverse effect on hypothalamic proopiomelanocortin gene across generations, Biol. Psychiatry 72 (2012) 378–388.
[154] L.N. Wei, H.H. Loh, Transcriptional and epigenetic regulation of opioid receptor genes: present and future, Annu. Rev. Pharmacol. Toxicol. 51 (2011) 75–97.
[155] H. Sun, I. Maze, D.M. Dietz, K.N. Scobie, P.J. Kennedy, D. Damez-Werno, R.L. Neve, V. Zachariou, L. Shen, E.J. Nestler, Morphine epigenomically regulates behavior through alterations in histone H3 lysine 9 dimethylation in the nucleus accumbens, J. Neurosci. 32 (2012) 17454–17464.
[156] M.R. Chao, D. Fragou, P. Zanos, C.W. Hu, A. Bailey, S. Kouidou, L. Kovatsi, Epigenetically modified nucleotides in chronic heroin and cocaine treated mice, Toxicol. Lett. 229 (2014) 451–457.
[157] J.A. DiNieri, X. Wang, H. Szutorisz, S.M. Spano, J. Kaur, P. Casaccia, D. Dow-Edwards, Y.L. Hurd, Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring, Biol. Psychiatry 70 (2011) 763–769.
[158] H. Szutorisz, J.A. DiNieri, E. Sweet, G. Egervari, M. Michaelides, J.M. Carter, Y. Ren, M.L. Miller, R.D. Blitzer, Y.L. Hurd, Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation, Neuropsychopharmacology 39 (2014) 1315–1323.
[159] T. Hillemacher, H. Frieling, V. Buchholz, R. Hussein, S. Bleich, C. Meyer, U. John, A. Bischof, H.J. Rumpf, Alterations in DNA-methylation of the dopamine-receptor 2 gene are associated with abstinence and health care utilization in individuals with a lifetime history of pathologic gambling, Prog. Neuropsychopharmacol. Biol. Psychiatry 63 (2015) 30–34.
[160] C. Dias, J. Feng, H. Sun, N.Y. Shao, M.S. Mazei-Robison, D. Damez-Werno, K. Scobie, R. Bagot, B. LaBonte, E. Ribeiro, X. Liu, P. Kennedy, V. Vialou, D. Ferguson, C. Pena, E.S. Calipari, J.W. Koo, E. Mouzon, S. Ghose, C. Tamminga, R. Neve, L. Shen, E.J. Nestler, beta-catenin mediates stress resilience through Dicer1/microRNA regulation, Nature 516 (2014) 51–55.
[161] J.J. Walsh, A.K. Friedman, H. Sun, E.A. Heller, S.M. Ku, B. Juarez, V.L. Burnham, M.S. Mazei-Robison, D. Ferguson, S.A. Golden, J.W. Koo, D. Chaudhury, D.J. Christoffel, L. Pomeranz, J.M. Friedman, S.J. Russo, E.J. Nestler, M.H. Han, Stress and CRF gate neural activation of BDNF in the mesolimbic reward pathway, Nat. Neurosci. 17 (2014) 27–29.
[162] Y.N. Ohnishi, Y.H. Ohnishi, V. Vialou, E. Mouzon, Q. LaPlant, A. Nishi, E.J. Nestler, Functional role of the N-terminal domain of DeltaFosB in response to stress and drugs of abuse, Neuroscience 284 (2015) 165–170.
[163] I.C. Weaver, N. Cervoni, F.A. Champagne, A.C. D'Alessio, S. Sharma, J.R. Seckl, S. Dymov, M. Szyf, M.J. Meaney, Epigenetic programming by maternal behavior, Nat. Neurosci. 7 (2004) 847–854.
[164] S. St-Cyr, P.O. McGowan, Programming of stress-related behavior and epigenetic neural gene regulation in mice offspring through maternal exposure to predator odor, Front. Behav. Neurosci. 9 (2015) 145.
[165] M. Manikkam, C. Guerrero-Bosagna, R. Tracey, M.M. Haque, M.K. Skinner, Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures, PLoS One 7 (2012) e31901.
[166] V. Hughes, Epigenetics: the sins of the father, Nature 507 (2014) 22–24.
[167] M. Manikkam, R. Tracey, C. Guerrero-Bosagna, M.K. Skinner, Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations, PLoS One 7 (2012) e46249.
[168] A. Ost, A. Lempradl, E. Casas, M. Weigert, T. Tiko, M. Deniz, L. Pantano, U. Boenisch, P.M. Itskov, M. Stoeckius, M. Ruf, N. Rajewsky, G. Reuter, N. Iovino, C. Ribeiro, M. Alenius, S. Heyne, T. Vavouri, J.A. Pospisilik, Paternal diet defines offspring chromatin state and intergenerational obesity, Cell 159 (2014) 1352–1364.
[169] T. Fullston, E.M. Ohlsson Teague, N.O. Palmer, M.J. DeBlasio, M. Mitchell, M. Corbett, C.G. Print, J.A. Owens, M. Lane, Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content, FASEB J. 27 (2013) 4226–4243.
[170] C.T. Watson, H. Szutorisz, P. Garg, Q. Martin, J.A. Landry, A.J. Sharp, Y.L. Hurd, Genome-wide DNA methylation profiling reveals epigenetic changes in the rat nucleus accumbens associated with cross-Generational effects of adolescent THC exposure, Neuropsychopharmacology 40 (2015) 2993–3005.
[171] E.E. Zumbrun, J.M. Sido, P.S. Nagarkatti, M. Nagarkatti, Epigenetic regulation of immunological alterations following prenatal exposure to marijuana cannabinoids and its long term consequences in offspring, J. Neuroimmune Pharmacol. 10 (2015) 245–254.
[172] X. Wang, D. Dow-Edwards, V. Anderson, H. Minkoff, Y.L. Hurd, In utero marijuana exposure associated with abnormal amygdala dopamine D2 gene expression in the human fetus, Biol. Psychiatry 56 (2004) 909–915.
[173] X. Wang, D. Dow-Edwards, E. Keller, Y.L. Hurd, Preferential limbic expression of the cannabinoid receptor mRNA in the human fetal brain, Neuroscience 118 (2003) 681–694.

[174] X. Wang, D. Dow-Edwards, V. Anderson, H. Minkoff, Y.L. Hurd, Discrete opioid gene expression impairment in the human fetal brain associated with maternal marijuana use, Pharmacogenomics J. 6 (2006) 255–264.
[175] B.E. Deverman, P.H. Patterson, Cytokines and CNS development, Neuron 64 (2009) 61–78.
[176] L.M. Boulanger, Immune proteins in brain development and synaptic plasticity, Neuron 64 (2009) 93–109.
[177] L.G. Green, J.L. Stein, G.S. Stein, Influence of delta 9-tetrahydrocannabinol on expression of histone and ribosomal genes in normal and transformed human cells, Bioch. Pharmacol. 33 (1984) 1033–1040.
[178] G.S. Stein, J.L. Stein, Effects of cannabinoids on gene expression, NIDA Res. Monogr. 44 (1984) 5–24.
[179] M.S. Spano, M. Ellgren, X. Wang, Y.L. Hurd, Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood, Biol. Psychiatry 61 (2007) 554–563.
[180] P.W. Lewis, C.D. Allis, Poisoning the histone code in pediatric gliomagenesis, Cell Cycle 12 (2013) 3241–3242.
[181] K. Hochedlinger, K. Plath, Epigenetic reprogramming and induced pluripotency, Development 136 (2009) 509–523.
[182] S. Horvath, DNA methylation age of human tissues and cell types, Genome Biol. 14 (2013) R115.
[183] R.R. Kanherkar, N. Bhatia-Dey, A.B. Csoka, Epigenetics across the human lifespan, Front Cell Dev. Biol. 2 (2014) 49.
[184] B.M. Turner, Cellular memory and the histone code, Cell 111 (2002) 285–291.
[185] I.B. Zovkic, B.S. Paulukaitis, J.J. Day, D.M. Etikala, J.D. Sweatt, Histone H2A.Z. subunit exchange controls consolidation of recent and remote memory, Nature 515 (2014) 582–586.
[186] A. Petronis, Epigenetics as a unifying principle in the aetiology of complex traits and diseases, Nature 465 (2010) 721–727.
[187] N.D. Volkow, R.D. Baler, W.M. Compton, S.R. Weiss, Adverse health effects of marijuana use, N. Engl. J. Med. 370 (2014) 2219–2227.
[188] W. Hall, M. Weier, Assessing the public health impacts of legalizing recreational cannabis use in the USA, Clin. Pharmacol. Ther. 97 (2015) 607–615.
[189] W. Hall, Getting to grips with the cannabis problem: the evolving contributions and impact of Griffith Edwards, Addiction 110 (Suppl. 2) (2015) 36–39.