CANNABIS

A General Survey of its Harmful Effects

Submission to The Social Justice Policy Group 2006
(Now called the CSJ, The Centre for Social Justice)

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Introduction

When I was asked to take charge of the Health Education Programme in my school about 20 years ago, I had limited knowledge of drugs and the damage they can do. Since cannabis was then, and still is, the most frequently used illegal drug I decided to find out as much as possible about it.

What I discovered all that time ago, shocked me, and ever since I have been trying to publicise the damage that this drug can do to the brains and bodies of its users.

Cannabis use has risen inexorably since 1981 when British Crime Survey data was first published. 1.75 million adults in Britain are estimated to have used cannabis in the last month. More worrying though is the 12% of 11 to 15 year olds who took it in the year 2004-2005, the year following down-classification. This was up by 1% (thousands more children) from the previous year.

Apart from the devastating consequences that mental illness brings to users and their families, many other harmful effects have been recorded. Various cancers, heart attacks and strokes, disruption to the reproductive processes, deficiencies in children born to cannabis-using mothers and impaired immune systems are all part of the sorry saga.

But what most concerned me as a teacher was the ruin of the careers of some of my pupils. Few children using cannabis even occasionally will achieve their full potential. Because the drug persists in the cell membranes literally for weeks, the functioning of the brain is permanently impaired even on one joint a month.

For all these reasons I have collected data on cannabis from many different sources and on many different aspects, including driving, the gateway theory and possible use in medicine. Well over 400 papers are referenced. There are many more. I hope this book will be useful to anyone, and especially those dealing with young children. The younger a child is when use starts, the more likely he or she is to develop a mental illness, become addicted or move on to other drugs. It is our duty as adults to protect them. They are our future.

Mary Brett 2006

Foreword I

The very word cannabis arouses opinions and emotions. There are few substances which are surrounded by more controversy, and which have at the same time such important and potentially far-reaching public health implications. Most of the evidence concerning cannabis and different aspects of health is clear, but not definitive, as it takes time to accumulate the detail that makes it apparent to everyone what are the likely outcomes of using a particular substance. In other words, we know what is likely to happen, but it is a question of "watch this space", before we know how it will affect society. For example, the excess mortality and healthcare costs associated with the use of tobacco and alcohol are well known, while those for cannabis remain largely unknown. Eventually there will be robust estimates which will aid healthcare workers and political decision-making, but for the moment we have to wait. This is especially true of cannabis because the baseline is difficult to establish – prevalence rates are changing, and so is the strength of the plant's active ingredients. At the same time, this lack of definitive evidence concerning the population is certainly not to be taken as a lack of evidence of harm for individuals.

Mary Brett has done us all a great favour by putting together a large amount of data concerning cannabis, and anyone who is teaching, researching, learning or just plain curious will find here a wealth of detail covering the different kinds of damage that cannabis is capable of causing. Because she has been following up the subject for several years, she has been able to put together a wealth of detail as it has evolved, which can only serve to be a great benefit to anyone who is interested in or concerned about the health implications of cannabis.

Professor John Henry
Clinical Toxicologist
St Mary's Hospital, Paddington, London.

Foreword II

The present renewed interest in cannabis is so great that anyone seeking to be well informed is likely to be overwhelmed by the burgeoning literature on the subject. Scarcely a week passes without a new publication on cannabis and cannabinoids and a new "revelation" in the media. Mary Brett is to be congratulated on providing an unbiased and comprehensive survey which encompasses most of the present knowledge of the harmful effects of cannabis and the issues that arise in education because of its widespread use, particularly in the young. She gives a clear, balanced and well referenced presentation of the published evidence, ranging from the effects of cannabis on cognitive function and educational performance, mental and physical health, to its effects on driving and its possible "gateway effect" into other recreational drugs. Writing from the perspective of a school science teacher, she contributes a well-argued chapter about drug education in UK schools which cogently refutes current "harm-reduction" approaches. This readable survey will be of value to all those interested in cannabis including users themselves and their parents, teachers, general practitioners and academics in search of a digest of recent references. The facts are presented in a form that is accessible both to specialists and to the general public.

Professor Heather Ashton
Honorary Consultant in Clinical Psychopharmacology
Newcastle University

The following have endorsed this submission:

Professor Heather Ashton, Emeritus Professor of Clinical Psychopharmacology, Newcastle University.

Professor Neil McKeganey, Professor of Drug Misuse Research, University of Glasgow.

Professor Eric Voth, MD, FACP, Chairman Institute on Global Drug Policy, Editor in chief, The Journal of Global Drug Policy and Practice.

Dr Ian Oliver, Former Chief Constable of both Central Scotland and Grampian Police, International Consultant on Drugs to the UN, Board member of the International Scientific and Medical Advisory Forum on Drug Abuse and an elected member of The Institute of Global Drug Policy.

Dr Michelle Tempest, Liaison Psychiatrist, Addenbrookes Hospital Cambridge.

Dr Hans-Christian Raabe, GP Manchester. Long-time Campaigner against Cannabis.

Dr Hans Koeppel MD, Psychiatrist, Swiss Doctors against Drugs. Chair of Scientific Board EURAD (Europe Against drugs).

Dr Anthony Seldon, Master, Wellington College, Berks.

Grainne Kenny, International President of EURAD (Europe Against Drugs). Trained Counsellor and Drug Educator.

Dennis Wrigley, Leader and co-founder, The Maranatha Community, Manchester. (The Maranatha Community has been deeply involved in helping young people with drug problems for over 25 years in many parts of the United Kingdom. Its thousands of members include doctors, scientists, teachers, social workers, counsellors, in addition to numerous voluntary workers).

Peter O'Loughlin, Director, The Eden Lodge Practice. Drug and Alcohol Recovery Specialist.

Debra Bell, Founder, Chair, 'Talking About Cannabis'.

Peter Walker, ex-Headteacher Abbey School, Faversham, Kent. Advisor to the Government on Drug Testing in Schools.

Dawn Lowe-Watson, Writer, Bereaved Parent.

Bill Cameron, President Drug-Free Scotland.

Quotes:

Professor Neil McKeganey: "I have found it to be a very useful summary of the evidence".

Professor Eric Voth: "This paper is excellent and valid, It is an excellent addition to understanding of the marijuana problem".

Professor Heather Ashton: "I use it as a reference all the time".

Grainne Kenny: "This is a very valuable paper and a must-read for anyone involved in drug policy. Mary Brett's documentation on scientific research into cannabis is much sought after throughout Europe. It is an ideal explanation and support for all of us who care about the future of our young people. The United Nations Convention (article 33) on the Rights of Children clearly states that, 'We must Protect all Children from the use of and involvement with Narcotic Drugs'. Cannabis is a narcotic drug. We cannot afford to ignore her findings".

Dr Hans Koppel: "This is a very valuable scientific-based paper, a good introduction and overview on cannabis and the consequences of its use. Cannabis is a narcotic drug in the sense of a psychoactive harmful substance with severe consequences to the brain function. This document is a very important help and enrichment for the difficult controversy on the cannabis problem. Congratulations!!"

Dr Ian Oliver: "A thoroughly accurate and well researched document which demonstrates beyond any argument to the contrary that cannabis is a dangerous drug".

Dr Michelle Tempest: "I work on the front line and deal with all A and E admissions. This covers all psychiatric illness (ages 17 - 65) and will often include patients who have been abusing drugs, frequently cannabis which can exacerbate mental illness. I am often the one on the front line having to explain to parents and children about the dangers and consequences of cannabis use".

Debra Bell: "Mary's work on cannabis is an invaluable tool for anyone who wishes to educate themselves on the dangers of cannabis, especially on the young. I have recommended it to all concerned parents and carers who have contacted our organisation as being the most up to date and informative document you can find today. Mary Brett is quite simply a phenomenon".

Dawn Lowe-Watson: "I am not a scientist and don't know whether it is possible or relevant for me as a parent to endorse Mary Brett's brave and brilliant work on the dangers of cannabis. I lost my eldest son to drugs. He died of heroin in 2000 and some of his last words to me were - "Don't ever smoke pot, mother dear!" This gifted man had been mentally ill for most of his adult life and locked in a secure ward for four of those. I said it was hardly likely. He always told me how the pot had made him paranoid and the pain turned him to heroin, cocaine and everything that eventually destroyed him".

Dennis Wrigley: "I strongly endorse this excellent survey and pay tribute to the great work of Mary Brett to help our young people whose lives are threatened by the scourge of cannabis.
Mary Brett is admired throughout the country for the accuracy of her scholarship as well as her compassion for those in need".

Cannabis: Introduction and General Facts

Cannabis – some very old papers:

Let's take a look at what physicians from a time untainted by politics, drug morality, or profit motive had to say about cannabis risks:

> "In large doses it will produce hallucinations, which, in some, are of merriment and in others of a violent nature, even tendency to crime… Its habitual use will cause insanity"
>
> *Materia Medica and Clinical Therapeutics*, by Fred Petersen, published in 1905
> The most common effect, however, is the development of insanities which have been known for many years… Chronic mania and dementia represent terminal stages"
>
> *A Textbook of Materia Medica, Pharmacology and Therapeutics*, by George F. Butler, published in 1908
> "Repeated use of the drug produces mental weakness and [mental] impotence, the result of over-stimulation."
>
> *A Compend of Materia Medica, Therapeutics, Prescription Writing: With Especial Reference to the Physiological Actions of Drugs*, by Samuel O.L. Potter, published in 1890
> "Sometimes the delirium induced by hemp causes the individual to do deeds of violence, but does not act upon all alike… The after-effects are those of depression."
>
> *Materia Medica and Therapeutics for Physicians and Students*, by John Biddle, published in 1895
> "Hallucinations occur, but they are not usually agreeable; they are often painful and are replaced by stupor… Not unfrequently the excitement takes the form of a furious delirium, in which acts of violence are committed – whence the name 'haschaschins,' or assassins, applied to the unfortunate hashish-eater who, under the influence of the drug, commits murder… Dilatation of the pupil, and disorders of vision, which contribute to the hallucinations by distortions of external objects, are produced by hemp"
>
> *A Practical Treatise on Materia Medica and Therapeutics*, by Roberts Bartholow, published in 1893
> "There is often a disposition to laugh, sing, shout, or dance, or to do some other extravagant act; but, in other instances, the excitement betrays itself in a quarrelsome temper or deeds of violence… Occasionally, a species of intoxication is induced, with hallucinations or complete delirium… Among those who use it habitually, it is said ultimately to impair the mental faculties"
>
> *A Treatise on Therapeutics, and Pharmacology, or Materia Medica*, by George B. Wood, published in 1868

Cannabis sativa grows well in tropical and temperate climates. Marijuana consists of the dried plant parts, Hashish is the resin secreted by glandular hairs all over the plant mainly round the flowers, protecting the plant from water loss. Sinsemilla is the dried material from the tops of the female plants. Hashish oil (up to 60% THC), is obtained by extraction but rarely used in the UK.

Cannabis contains some 400 chemical substances. These vary with the habitat and are often contaminated with microbes, fungi or pesticides (Jenike 1993, BMA 1997). More than 60 cannabinoids, substances unique to the plant have been identified. The most psychoactive of these and the main cause of many of the other harmful pharmacological effects is THC (delta-9-tetrahydrocannabinol) (Ranstrom 2003). Other natural cannabinoids are delta-8-THC, cannabinol and cannabidiol (BMA 1998).

Brain signals pass along nerve cells in the form of electrical impulses, and chemicals called neurotransmitters carry the messages between cells. These dozens of neurotransmitters are released at the end of one neuron (nerve cell) and fit into receptor sites by shape on the next cell. Transmission of nerve signals takes a fraction of a second. The psychoactive THC mimics a neurotransmitter called anandamide and so affects its receptor sites (Devane et al, 1992).

Two types of receptor site have been identified, CB1 receptors are distributed in the brain in the areas concerned with motor activity and control of posture (cerebellum and basal ganglia), emotion (amygdala and hippocampus), memory, cognition, the "high", distortion of the sense of time, sound, colour and taste, the alteration of the ability to concentrate and the production of a dreamlike state (cerebral cortex and hippocampus), sensory perception (thalamus), mood in general and sleep. No CB1 receptors are present in the brain stem so the drug does not affect basal bodily functions like respiration. This explains the lack of deaths by overdosing with cannabis (Harkenham et al, 1991, 1992, BMA 1997). CB2 receptors were discovered in 1994 by Lynn and Harkenham. They were outside the brain on specific components of the

immune system. Binding of cannabinoids was also seen in the heart, lungs, endocrine and reproductive systems, so all these systems are affected.

Cannabinoids are absorbed rapidly into the body after inhalation from smoked cannabis preparations. The effects become noticeable in a matter of minutes. They are then rapidly distributed all over the body and maximum brain concentrations are reached within 15 minutes. The psychological effects can last for 2 to 4 hours then slowly decline over the next 12 hours. When taken orally, THC absorption is much slower and more variable and the onset of its effects are delayed by 30 minutes to 2 hours. The duration of its effects are prolonged, 5 to 6 hours due to continued absorption from the gut and some cognitive and motor skills are impaired for much longer e.g. driving. (Huestis et al 1992, BMA 1997). Cannabis can cross the placenta, enter the circulation of the foetus and pass into breast milk.

Cannabinoids are highly lipid-soluble and so rapidly accumulate in the fatty tissues, being slowly released back into other body tissues and organs including the brain and bloodstream. Elimination of a single dose can take 30 days, unlike water-soluble alcohol which is removed at the rate of one unit per hour, and appears in the faeces and urine. Repeated doses will therefore accumulate in the body and affect the brain over long periods of time (BMA 1997). Cannabis is a multi-faceted drug. The inhibitory effects of THC on the release of a variety of neurotransmitters in the central nervous system has also been observed in several studies (Schliker and Kathmann, 2001, Katona et al 2000). Blood levels of THC drop rapidly after smoking due to its conversion into metabolites and sequestration into fatty tissues (Grotenhermen 2003).

Since 1971 when drugs were classified and cannabis was consigned to class B, the amount of THC in the plant in some varieties of Cannabis sativa has changed considerably. At that time the content of THC in marijuana was around 0.5 – 3% (Ranstrom 2003), <1% (UNODC figs). Smokers in the late 80s and 90s had access to sensemilla (7 to 11% THC, Schwartz 1991). Hashish has consistently had a THC content of 4 to 5%. However, selective breeding of the plant, especially in Holland, has produced varieties such as Netherweed and Skunk with THC contents up to and over 20% (Jenike, 1993, BMA 1998).These stronger types, now commonly grown in the UK are favoured by today's users, the lower levels being much less common (Ranstrom 2003). An article in The Guardian on 29th August 2006 reported that "Analysis of recent home-grown hauls detected THC levels as high as 20%, nearly 7 times higher than samples of imported resin, which used to be the predominant form of the drug on the streets, and typically contained around 3% THC" Detective Inspector Neil Hutchison said, "A decade ago 11% of the cannabis sold on the street was grown in the UK. Now more than 60% is produced in Britain …". The Forensic Science Service, Drugs Intelligence Unit confirmed this figure (10/10/06) and said that between 30 and 40% of the rest is imported resin, some imported herbal cannabis is still seen as well. At a meeting of the Science and Technology Committee of the House of Commons on 22nd November 2006, Dr Brian Iddon MP said that 70% of the cannabis in the UK is home grown and is skunk. The discovery of a new high-potency hybrid known as "Colombian" in December 2006 in Mexico has sent alarm bells ringing. It can be planted at any time of year and matures in 2 months. Worse than that, it cannot be killed by pesticides. A plot the size of a football field yields as much as was formerly grown on a 10 to 12 acre plot (Associated Press, Mark Stevenson 20/12/06). A Home Office Cannabis Potency Study in 2008 found that seizures in early 2008 were 80.8% herbal and 15.3% resin, the rest (3.9%) were indeterminate or not cannabis. Over 97% of the herbal cannabis was sinsemilla, the remainder imported traditional. The mean potency of the sinsemilla was 16.2% (range 4.1 to 46%). The mean potency of the imported herb was 8.4% (range 0.3% to 22%) but accounted for very few samples. Mean potency of cannabis resin was 5.9%, similar to previous years.

1985 Ellis et al looked at excretion patterns of cannabinoid metabolites after last use in a group of 86 chronic users. 'We demonstrated that under very strictly supervised abstinence, chronic users can have positive results for cannabinoids in urine at 20 ng/ml or above on the EMIT-d.a.u. assay for as many as 46 consecutive days from admission, and can take as many as 77 days to drop below the cut off calibrator for 10 consecutive days. For all subjects, the mean excretion time was 27 days. Subject excretion patterns were clearly biphasic, with initial higher rates of excretion not sustained. During the subsequent period of leveling off, most subjects had one or more separate sequences of cannabinoid-negative urine test results, lasting a mean of 3 days each and followed by at least one positive result. Demographic, body type, and drug history variables proved to be only moderate predictors of excretion patterns. Findings were discussed in the context of potential clinical and forensic application'.

1988 Hamadeh et al looked at fatal aspergillosis associated with smoking contaminated marijuana in a bone-marrow recipient. 'A 34-year-old man presented with pulmonary aspergillosis on the 75th day after marrow transplant for chronic myelogenous leukemia. The patient had smoked marijuana heavily for several weeks prior to admission. Cultures of the marijuana revealed Aspergillus fumigatus with

morphology and growth characteristics identical to the organism grown from open lung biopsy specimen. Despite aggressive antifungal therapy, the patient died with disseminated disease. Physicians should be aware of this potentially lethal complication of marijuana use in compromised hosts'.

2000 Congenital Anomaly Register & Information Service found that the incidence of gastrochisis doubled from 0.67 in 1987 to 1.35 per 10,000 of total births in 1991. Known risk factors include younger mothers, first babies, socially disadvantaged groups, mothers who smoke or use illegal drugs. Wales (40 cases in 1998) had a more significantly higher rate than England and Wales (103 in 1998) as a whole. Marijuana and cannabis/amphetamines are mentioned.

On 25th April 2007, the ONDCP (Office National Drug Control Policy) and NIDA (National Institute on Drug Abuse) issued the latest analysis from the University of Mississippi's Potency Monitoring Project that the highest ever levels of THC had been found since analysis began in the late 1970s. The average amount of THC in seized samples is 8.5%, up from 7% in 2003, in 1983 the average was under 4%. More than 60% of teens receiving treatment for drug abuse or dependence report marijuana as their primary drug of abuse. In 2005 the number of marijuana-related hospital emergency room admissions was 242,200 up from 215,000 in 2004. The highest concentration found in a sample was 32.3%. Roughly 60% of first-time marijuana users are under 18 in the USA.

Moir et al reported that cannabis smoke not only contains about 50 substances that can cause cancer but also 20 times more ammonia (linked to cancer) than tobacco smoke. Hydrogen cyanide (linked to heart disease), nitrogen oxides (linked to lung damage) and certain aromatic amines were at levels 3 to 5 times more.

It should be mentioned that cannabis research is still very young. In 1996 the total number of scientific papers did not exceed 10,000 and today probably stands between 14 and 15,000. This is in contrast to research on tobacco with about 140,000 studies to date (Ranstrom 2003). The total collection of scientific papers on cannabis is held in the library of The University of Mississippi.

A new type of cannabis product was reported by Drug Watch International on 25th February 2008. It is called "Budder". It is reported as being the purest cannabis product available at anywhere between 82 and 99.6% pure THC/CBD/CBN. One hit is equalled to 1 to 2 full cannabis joints and the "high" to be clearer and more long-lasting than average marijuana. Inhalation is the method of choice. A miniscule amount (head of pin) is applied to heated metal and inhaled. Major effects usually subside in 3 to 4 hours, others up to 8 hours. Hallucinations, paranoia, disconnection and hunger can all be felt. It is extremely mpotent and its effects can be delayed, leading some users to 'over consume' and be overwhelmed. It is made by whipping in air and freezing isomerized hash oil. The delta –9-THC is converted to delta-6-THC so normally inactive cannabinoids are activated.

A paper in 2005 by Pijlman and others found a considerable increase in the levels of THC in cannabis sold in Dutch coffeee shops. In 2004, the average level of THC in home grown Dutch marijuana (Nederwiet) was 20.4%, significantly higher than that of imported marijuana at 7%. Dutch hashish (Nederhasi) contained 39.3% THC in 2004 compared with 18.2% in imported hashish. The average percentage of THC in Dutch marijuana, Dutch hashish and imported hashish had almost doubled since 1999. It had remained consistent in imported marijuana.

2007 Forrester et al Documented the risk of selected birth defects with prenatl illicit drug use in Hawaii from 1986 t0 2002. 'The objective of this study was to determine the risk of a variety of birth defects with prenatal illicit drug use. Data were derived from an active, population based adverse pregnancy outcome registry. Cases were all infants and fetuses with any of 54 selected birth defects delivered during 1986–2002. The prenatal methamphetamine, cocaine, or marijuana use rates were calculated for each birth defect and compared to the prenatal use rates among all deliveries. Among all deliveries, the prenatal use rate was 0.26% for marijuana.. Marijuana rates were significantly higher than expected for 21 (39%) of the birth defects. Increased risk for the three drugs occurred predominantly among birth defects associated with the central nervous system, cardiovascular system, oral clefts, and limbs. There was also increased risk of marijuana use among a variety of birth defects associated with the gastrointestinal system. Prenatal uses of methamphetamine, cocaine, and marijuana are all associated with increased risk of a variety of birth defects.

2008 Home Office Cannabis Potency Study. 80.8% seizures were 'skunk', 15.3% resin. THC content of skunk was 16.2% ranging from 4.1 to 46%, resin (hashish) 5.9% THC, ranging from 1.3 to 27.8%.

CBD in resin was 3.5% but in skunk was lees than 0.1%.

2008 Moir et al compareed mainsteam and sidestream marijuana and tobacco cigarette smoke.
The chemical composition of tobacco smoke has been extensively examined, and the presence of known and suspected carcinogens in such smoke has contributed to the link between tobacco smoking and adverse health effects. The consumption of marijuana through smoking remains a reality and, among youth, seems to be increasing. There have been only limited examinations of marijuana smoke, including for cannabinoid content and for tar generation. There have not been extensive studies of the chemistry of marijuana smoke, especially in direct comparison to tobacco smoke. In this study, a systematic comparison of the smoke composition of both mainstream and sidestream smoke from marijuana and tobacco cigarettes prepared in the same way and consumed under two sets of smoking conditions, was undertaken. This study examined the suite of chemicals routinely analyzed in tobacco smoke. As expected, the results showed qualitative similarities with some quantitative differences. In this study, ammonia was found in mainstream marijuana smoke at levels up to 20-fold greater than that found in tobacco. Hydrogen cyanide, NO, NO x , and some aromatic amines were found in marijuana smoke at concentrations 3-5 times those found in tobacco smoke. Mainstream marijuana smoke contained selected polycyclic aromatic hydrocarbons (PAHs) at concentrations lower than those found in mainstream tobacco smoke, while the reverse was the case for sidestream smoke, with PAHs present at higher concentrations in marijuana smoke. The confirmation of the presence, in both mainstream and sidestream smoke of marijuana cigarettes, of known carcinogens and other chemicals implicated in respiratory diseases is important information for public health and communication of the risk related to exposure to such materials.

2010 Another report into concentrations of THC in Dutch marijuana was conducted for 2009 –2010 by The Netherlands Institute of Mental Health and Addiction (The Trimbos Institute). Random samples, sinsemilla (Nederwiet), imported marijuana, Dutch hash and hash from imported marijuana and the most potent herbal (202) were bought from Coffee shops. The average THC content of all samples was 16.7%, and 22% in the hash samples. Average THC of Nederwiet was 17.8% imported marijuana 7.8%. Hash from Dutch hemp had more (32.6%) than hash from foreign cannabis (19.0%).Average THC in Nederwiet was higher in 2010 than 2009 (17.8 cf 15.1%). THC in foreign marijuana was lower than year before (7.5% in 2010 and 9.9% in 2009). Average most potent 17.9%. Nederwiet had considerably less CBD than imported marijuana.

The average THC content of skunk (over 80% of the UK market now) is around 18%.

A new “form” of cannabis, SPICE (JWH-018), is being used by young people, and was legal in the UK. This is a synthetic psychoactive substance, created by an American academic purely for research purposes in 1995. According to The Royal Society of Chemists, it gives a “marijuana-like high” and is said to be 4 to 5 times stronger than THC. The chemical is added to packets of herbs, all legal. The structure of spice is quite different from THC but it has the same effects. It has already been banned in Holland, Austria, Germany and Switzerland. It was banned in the UK in December 2009.

In July 2010 Alexandra Datig found several very harmful fungi asssociated with marijuana. Black mould, Stachybotrys, exists on almost all building materials. The growth of cannabis indoors poses a great problem as it provids ideal conditions. Also the 3 most dangerous strains of Aspergillus, fumigitus, flavus and niger exist naturally on the plant. A deadly afla-toxin could be the result. A 1996 treatment study by Withenshawe Hospital, Manchester, on 10,000 patients with invasisve Aspergillosis has shown $633m in costs, average $63,300/patient to treat not cure the disease.

2010 Spano et al looked at cannabinoid-opioid interactions in drug discrimination and self-administration: effect of maternal, postnatal, adolescent and adult exposure to the drugs. **Abstract:** Cannabinoids and opioids are known to strictly interact in many physiological and pathological functions, including addiction. The endogenous opioid system is significantly influenced by maternal or perinatal cannabinoid exposure, major changes concerning operant behaviour in adult animals. Copious data suggests that adolescence is also a particularly sensitive period of life not only for the initiation of abusing illicit drugs, but also for the effects that these drugs exert on the neural circuitries leading to drug dependence. This paper examines the role played by the age of drug exposure in the susceptibility to discriminative and reinforcing effects of both cannabinoids and opioids. We first revisited evidence of alterations in the density and functionality of mu-opioid and CB1 cannabinoid receptors in reward-related brain regions caused by either maternal, postnatal, adolescent or adult exposure to opioids and cannabinoids.Then, we reviewed behavioural evidence of the long-term consequences of exposure to opioids and cannabinoids during gestation,postnatal period, adolescence or adulthood, focusing mostly on

drug discrimination and self-administration studies. Overall, evidenceconfirms a neurobiological convergence of the cannabinoid and opioid systems that is manifest at both receptor and behavioural levels.Although discrepant results have been reported, some data support the gateway hypothesis that adolescent cannabis exposure contributes to greater opioid intake in adulthood. However, it should be kept into consideration that in humans genetic, environmental, and social factors could influence the direct neurobiological effects of early cannabis exposure to the progression to adult drug abuse.

In 2010, Arendt et al published mortality figures among 20,581drug users over a 10 year period (1996-2006) in Denmark. 1441 deaths were recorded in follow-up (111,445 person years). Standardised Mortality Ratios (SMRs) for primary users of specific substances were, cannabis 4.9, cocaine 6.4, amphetamine 6.0, heroin 9.1 and otheropioids 7.7. For ecstasy the crude mortality rate was 1.7/1000 person years.

March 2011 ASReece published 'Chronic Toxicology of Cannabis.' 5198 papers were screened by hand and preferentially include the most recent ones.

FINDINGS: There is evidence of psychiatric, respiratory, cardiovascular, and bone toxicity associated with chronic cannabis use. Cannabis has now been implicated in the etiology of many major long-term psychiatric conditions including depression, anxiety, psychosis, bipolar disorder, and an amotivational state. Respiratory conditions linked with cannabis include reduced lung density, lung cysts, and chronic bronchitis. Cannabis has been linked in a dose-dependent manner with elevated rates of myocardial infarction and cardiac arrythmias. It is known to affect bone metabolism and also has teratogenic effects on the developing brain following perinatal exposure. Cannabis has been linked to cancers at eight sites, including children after in utero maternal exposure, and multiple molecular pathways to oncogenesis exist.
CONCLUSION: Chronic cannabis use is associated with psychiatric, respiratory, cardiovascular, and bone effects. It also has oncogenic, teratogenic, and mutagenic effects all of which depend upon dose and duration of use.

2011 Abrams et al investigated Cannabinoid-Opioid Interaction in chronic pain. Abstract: Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

2011 Accidental poisoning in children was reported in 4 cases in a care centre in Southern Spain by Croche Santander B et al. Paediatric accidental cannabis poisoning is an uncommon but life-threatening intoxication. Reduced level of consciousness, drowsiness, ataxia, tremble, apnea, hypotonia and seizures were all witnessed. THC was detected by urine screening. All recovered and were discharged within 24 hours. They concluded that the possibility of cannabis poisoning should be considered in unexplained acute onset of neurological findings in previously healthy children.

In 1981, the WHO Report on Cannabis Use said, "It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, "risk factors" have been freely identified, although full causality has not yet been established. Nevertheless such risk factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is often not applied to cannabis". ….. "To provide rigid proof of causality in such investigations is logically and theoretically impossible , and to demand it is unreasonable".

Updated information on THC concentration in weed, netherweed and hash in Dutch coffee shops 2010 to 2011. Frans Koopmans, De Hoop Clinic, Dordrecht, Netherlands.

Since the nineteen seventies the policy on cannabis use in The Netherlands has substantially been different from that in many other countries. It is based on the idea that separating the markets for hard and soft drugs prevents cannabis users to resort to hard drug use. Over the years so-called coffeeshops emerged. Coffeeshops are alcohol free establishments where the selling and the use of soft drugs is not prosecuted, provided certain conditions are met. Many of the cannabis products sold in these coffeeshops originate from Dutch-grown grass called 'nederwiet'. On behalf of the Ministry of Health, Wellfare and Sports we investigate the potency of cannabis products as sold in coffeeshops in The Netherlands.

Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive compound in marihuana and hashish. The aim of this study is to investigate the concentration of THC in marihuana and hash (=cannabis resin) as sold in Dutch coffeeshops. In addition we examined whether there are differences between the cannabis products originating from Dutch grown hemp (nederwiet) and those derived from imported hemp. This is the twelfth consecutive year that this study has been performed. Apart from THC, the content of two other cannabinoids, cannabidiol (CBD) and cannabinol (CBN), are measured.

The names and addresses of 50 (out of a total of 666) Dutch coffeeshops were randomly selected. For the purpose of this study, 65 samples of nederwiet, 19 samples of imported marihuana, 9 samples of Dutch hash and 56 imported hash samples were anonymously bought in the selected coffeeshops. In addition, 49 samples of the most potent (herbal) marihuana product available were bought. As a rule samples of 1 gram were bought. Samples were bought anonymously.

Traditionally hash contains more THC than marijuana. The average THC-content of all the marihuana samples together was 15,3% and that of the hash-samples 16,5%. The average THC-content of nederwiet (16,5%) was significantly higher than that of the imported marihuana (6,6%). The average THC-percentage of the marihuana samples that were bought as most potent (17,0%) did not differ from that of the most popular varieties of nederwiet (16,5%). Hash derived from Dutch hemp contained more THC (29,6%) than hash originating from foreign cannabis (14,3%). The average THC-percentage of nederwiet was lower in 2011 than in 2010 (16,5 vs. 17,8%), but this difference was not statistically significant. The THC-percentage in imported hash was significantly lower than the year before (14,3% in 2011 versus 19,0% in 2010).

There is some evidence that not only THC-content is indicative for the effects and risks of cannabis, but that CBD might attenuate some of the negative effects of THC. This means that cannabis with a high CBD / THC ratio would have less negative health consequences than cannabis that has little or no CBD. Nederwiet has very low levels of CBD (median = 0,3%), whereas imported hash contained on average 6,7% CBD.

The ratio between CBN and THC can give an indication of the freshness of the preparation (Ross and Elsohly, 1997). Levels of CBN were higher in imported marihuana and hash compared to products derived from homegrown cannabis. Also the ratio of CBN/THC was significantly higher in the imported products. The ratio was higher in imported marijuana compared to nederwiet and in imported hashish as compared to hashish made from nederwiet. Prices that had to be paid for imported marihuana were lower than those for any of the other cannabis products. The prices of hash made from nederwiet were higher. The average price for a gram nederwiet increased from 2007 to 2009 (up to 50%), but since then prices remained the same. On average, a gram of nederwiet costs €8,30.

2012 Mason et al Treatment for cannabis addiction. Gabapentin, on the market to treat neurpathic pain and epilepsy, helps people to quit marijana use. 50 treatment –seeking users taking gabapentin experienced fewer withdrawal symptoms, smoked less weedand scord higher on cognitive skills compared with those who had placebos. In the last 4 weeks of the study all gabapentin users were cannabis free.

2012 Crippal and others looked at medicines to reduce intoxication (euphoria, disturbed perception, giggling, red eyes, dry mouth, increased appetite, increased heart rate,misperception of time etc). A recent incease in the number of emergency room visits for marijuana intoxication prompted researchers to look for medical treatment. Propanolol used to treat cardiac conditions reduced several symptoms in well-done studies.

2012. Simonetto et al investigated cannabinoid hyperemesis in 98 patients who met the inclusion criteria ie recurrent vomiting and no other explanation but that of cannabis use. All were under 50, most had used cannabis for 2 years and more than once/week. Abdominal pain was common and hot baths/showers provided almost universal relief. They concluded, ' Cannabinoid hyperemesis should be considered in younger patients with long-term cannabis use and recurrent nausea, vomiting and abdominal pain.

2012 Agrawal et al discovered that a combination of tobacco and marijuana (common practice in USA now, about 50% of marijuana users e.g. as 'blunts') may be reacting to some unidentified mechanism that links the two drugs. 'there may be something about marijuana use that seems to worsen marijuana use in some way' said Erica Peters of Yale. It may it is thought be a genetic predisposition. In the few studies available, it appears that quitting both substances together at the same time is better. Quitters said the dual abstinence was less severe than from either drug alone.

2013 Kiriski looked at age of first time use of alcohol and cannabis to a transmissible risk for addiction in childhood and development of alcohol use disorder (AUD) and cannabis use disorder (CUD). They found that whereas transmissible risk is congenerous to both AUD and CUD, its magnitude is 7 times greater in youths who initiated substance use with cannabis. The earlier they started, the greater the risk.

2013 Chueh et al looked at factors involved in the resistence of substance abuse. They found that 'Being female, having strong knowledge about the substance, and negative attitude towards substance use correlated with higher levels of self-confidennce to resist substance use.

2013 June Bostwick found that medical marijuana use for pain may interfere with normal development. 3 high school age patients attended Mayo Clinic's chronic pain clinic. They were using cannabis for severe pain after everything else had failed. They reported worsening of the pain and impaired functioning. All 3 dropped out of school and social lives.

2013 May. Wang and others found no admissions of children under 12 for marijuana ingestion at a Colorado children's hospital before September 30th 2009, but 14 afterwards. 9 had lethargy, 1 ataxia, 1 respiratory insufficiency. 8 were admitted, 2 to intensive care. Eight of the 14 cases involved medical marijuana and 7 of these exposures were from food products.

2013 Harrison et al looked at chronic non malignant pain in adolescents. 3 cases of using medical marijuana were studied. None relieved the pain. They concluded that 'Even short-term marijuana use may be associated with health and cognitive concerns that may prevent adolescents from achieving their full academic and vocational potential.

2013 Chittamma et al found that umbilical cord tissue was a viable specimen for the detection of maternal use of marijuana.

2013 Hurd et al looked at the effects of cannabis through generations of male inheritance. Metabolic and behavioural effects of cannabis in rats during adolescence were passed down to multiple generations of male offspring, even though these animals were not themselves exposed to the drug.

2013 Dec Wu and others found that cannabis use disorders (CUD) are comparatively prevalent among non-white racial/ethnic groups and adolescents in the USA. In USA, non-white population is growing faster than the whites. All confounding issues were controlled for. Compared with whites, mixed-race people had higher incidences of CU (Cannabis Use), Asian Americans and Hispanics had a lower incidence. Past-year cannabis users who were black, Native American, Hispanic or Asian American had higher odds of CUD than whites, in all ethnic groups, adolescents had higher odds than adults. Major depressive episodes, arrest history, nicotine dependence, alcohol disorder, were all associated with CU and CUDs. CUD disproportionately affects non-white groups and adolescents.

2013 Yetisan et al looked at Holographic Diagnostics in Medicine. 'Smart' holographs are used to detect various substances (including drugs) by turning colour in their presence. They are being researched at Addenbrooke's Hospital in Cambridge. In the presence of of certain compounds, the hydrogels either shrink or swell, causing the holograph to change colour. The process is fast, cheap and easy to use.

2013 Heron et al looked at prior cannabis risk factors and use at 16. Over 4,000 children provided information at the age of 16 in The Avon Longitudinal Study of parents and Children. They found that

cannabis use was more common in girls than boys, 21.4% v 18.3%. Problem cannabis use in boys was higher than girls, 3.6% v 2.8%. Early onset persistent conduct problems were strongly associated with problem cannabis use, odds ratio (OR) 6.46. Residence in subsidised housing, OR 3.10, maternal cannabis use, 8.84, any maternal smoking in the post- natal period 2.69, all predicted problem cannabis use. Attributable risks for adolescent problem cannabis use associated with the previous factors was 25, 13, 17 and 24% respectively.

2013 Huang and others looked at adolescent substance use and obesity in young adulthood. 5141 adolescents were taken from the child sample of the 1979 National longitudinal Survey of Youth and biennial data across the 12 assessments from 1986 to 2008 was used. Cigarette smoking, alcohol use and marijuana use from age 12 to 18 and obesity trajectories from ages 20-24 were examined. Adolescents with the most problematic smoking trajectory, and those with an increasing marijuana trajectory were most likely to exhibit an increased obesity trajectory in young adulthood.

2013 Public Health Agency of Canada published 'Congenital Abnormalities in Canada 2013. Findings included evidence of congenital heart defects and an ODDS Ratio for gastroschisis of 3.0

2013 Morgan et al looked at cerebrospinalfluid anandamide levels, cannabis use and psychotic-like symptoms. Abstract: Anandamide is a ligand of the endocannabinoid system. Animals show a depletion following repeated Δ(9)-tetrahydrocannabinol (THC) administration but the effect of cannabis use on central nervous system levels of endocannabinoids has not been previously examined in humans. Cerebrospinal fluid (CSF) levels of the endocannabinoids anandamide, 2-arachidonoylglycerol (2-AG) and related lipids were tested in 33 volunteers (20 cannabis users). Lower levels of CSF anandamide and higher levels of 2-AG in serum were observed in frequent compared with infrequent cannabis users. Levels of CSF anandamide were negatively correlated with persisting psychotic symptoms when drug-free. Higher levels of anandamide are associated with a lower risk of psychotic symptoms following cannabis use.

2014 Vallee et al discovered that pregnenolone can protect the brain from cannabis intoxication. Pregnenolone is the inactive precursor of all steroid hormones. THC substantially increases the synthesis of pregnenolone in the brain via activation of the CB1 receptor. Pregnenolone then acting as a signalling specific inhibitor of the CB1 receptor reduces several effects of THC. This negative feedback protects the brain from CB1 receptor over-activation. This may open an approach for the treatment of cannabis intoxication and addiction.

2 014 Wolff K Smoking infrequently a single cannabis cigarette leads to peak plasma concentrations of 21-267 micrograms/litre causing acute intoxication. Daly users the plasma THC concentrations are 1.0-11.0 micrograms/litre maintained by sequestration of the drug from the tissues.

2014 Hall and Degenhardt updated and summarised the most harmful effects of cannabis. They listed the most probable of the adverse health effects of regular cannabis use sustained over the years as indicated by epidemiological studies that have established the links. These are: dependence syndrome, impaired respiratory function, cardiovascular disease, adverse effects on adolescent psychosocial development and mental health, and residual cognitive impairment.

2014 Cooper and Haney looked at sex-dependent effects of cannabis in daily smokers. 35 men and 35 women were studied. Women reported higher ratings of abuse-related effects ('take again', 'good' 'liked it') relative to men but not in intoxication . Increased heart-rate similar in both sexes. They concluded that women are more sensitive to the subjective effects related to cannabis' use liability relative to men which may contribute to the enhanced vulnerability to developing Cannabis Use Disorders (CUDs).

2014 Hartung et al Looked at cannabis as a cause of death. They conducted post-mortems on 15 people whose deaths were linked to cannabisa use. Other factors that might have contributed to the death, alcohol, liver disease etc were discounted. Two of the deaths could not be attributed to anything else but cannabis intoxication. Both men died of cardiac arrhythmia triggered by cannabis, and had enough active THC in their blood to show they had taken it recently. Neither had a history of heart problems.

2014 Feb Capretto warned parents of a new drug '10' times more potent than marijuana.. BHO, Butane Honey Oil, or Dab is made by extracting THC and the use of household items eg butane containers, glass or metal tubes, baking dishes and even coffee filters.

2014 April 2nd BBC News (Canada and US) reported the first death due to cannabis in Colorado since legalisation. An exchange student fell to his death after ingesting edible marijuana. A Post Mortem examination found marijuana intoxication was a factor in the death.

2014 June Chheda et al found sleep to be affected by cannabis use. Results showed that any history of cannabis use was associated with an increased likelihood of reporting difficulty in falling asleep, struggling to maintain sleep, experiencing non-restorative sleep and feeling daytime sleepiness. The strongest association was found in those who started early, before 15 being about twice as likely to have severe problems, and to have sleep problems as adults.

2014 Danielsson et al found that heavy pot use in teen years may predict later-life disability. Those who smoked heavily at 18 were most likely to end up on the nation's (Sweden) disability rolls by 59. The Swedish cohort of 98% of the male population (conscripts) at baseline and a 39 year long follow up time provided new knowledge. Men who had used marijuana more than 50 times before the age of 18 were 30% more likely to go on disability sometime between 40 and 5 years of age.

2014 June Volkow (NIDA) et al wrote an update on Adverse Health Effects of marijuana Use in The New England Journal of medicine

2014 Correspondence followed the article by Volkow and others.

2014 July Voss et al investigated the detection of cannabis use on the human skin via an electronic nose system. Their study produced evidence that a low-cost portable and fast-working E-Nose system could be useful for health protection, security agents and forensic investigations. There are implications for diagnosis of other drugs and even diseases.

2014 Stone looked at the presence of pesticides on legalized marijuana. Large yields of high quality plants are desirable so pesticides may be used by legal growers to achieve this aim. Currently there are no pesticides registered for cannabis in the USA due to its illegal status. Pesticide use presents occupational safety issues for workers. The absence of approved products for cannabis may well result in consumer exposures to otherwise more hazardous pesticides or higher residue levels.

2014 August Palamar et al investigated hookah use among US high school seniors. Prevalence of hookah use is increasing significantly among adolescents. The hypothesis was that impoverished adolescents and cigarette smokers would use hookahs. 5540 high school seniors were monitored. 18% of students used hookahs in the last year. High parent education and money (from weekly jobs), males and urban students, users of alcohol, marijuana and other illicit substances, former tobacco smokers were at higher risk and current smokers at highest risk.

2014 Cone et al looked at non-smoker exposure to second-hand cannabis smoke. Six experienced cannabis users smoked cannabis cigarettes (5.3% THC in session 1 and 11.3% in sessions 2 and 3) in a sealed chamber with no ventilation in sessions 1 and 2 but with ventilation in session 3. Six non-smokers were seated in an alternating manner. THCCOOH concentrations generally increased with THC potency but ventilation substantially reduced exposure levels. They concluded that positive tests are likely to be rare, limited to the hours immediately post-exposure and occur only under environmental circumstances where exposure is obvious.

Wayne Hall, 2 014 October, wrote an extremely important paper on the adverse health effects of cannabis. This is the abstract.

Aims To examine changes in the evidence on the adverse health effects of cannabis since 1993.
Methods A comparison of the evidence in 1993 with the evidence and interpretation of the same health outcomes in 2013.
Results Research in the past 20 years has shown that driving while cannabis-impaired approximately doubles car crash risk and that around one in 10 regular cannabis users develop dependence. Regular cannabis use in adolescence approximately doubles the risks of early school-leaving and of cognitive impairment and psychoses in adulthood. Regular cannabis use in adolescence is also associated strongly with the use of other illicit drugs. These associations persist after controlling for plausible confounding variables in longitudinal studies. This suggests that cannabis use is a contributory cause of these outcomes but some researchers still argue that these relationships are explained by shared causes or risk factors. Cannabis smoking probably increases

cardiovascular disease risk in middle-aged adults but its effects on respiratory function and respiratory cancer remain unclear, because most cannabis smokers have smoked or still smoke tobacco. **Conclusions** The epidemiological literature in the past 20 years shows that cannabis use increases the risk of accidents and can produce dependence, and that there are consistent associations between regular cannabis use and poor psychosocial outcomes and mental health in adulthood.

2014 Dec. Pelissier et al looked at accidental intoxications in children. The number of children under 6 hospitalised for cannabis poisoning in a paediatric emergency department from 2007 to November 2012 were retrospectively evaluated. Twelve toddlers (4 boys, 8 girls, mean age 16.6 months) were included, all had ingested cannabis. Seven children experienced drowsiness or hypotonia. Three were given activated charcoal. Blood screening for cannabinoids was negative in two cases, urine samples positive in seven (70%). All had favourable outcomes after 2 to 48 hours hospitalisation. Nine were referred to social services before discharge. They concluded that cannabis intoxication in children should be reported to child protection services with the aim of prevention. Legal action may be considered.

2014 Nov Lanaro et al determined the amount of herbicides present in marijuana. Paraquat was detected in 12 samples (n=130), ranging from 0.01 to 25mg/g. Three samples were positive for glyphosphate (0.15-0.75mg/g) and one sample had AMPA (aminomethylphosphonic acid) as well.

2014 Nordholm-Carstensen A abstract: Cannabinoid hyperemesis syndrome (CHS) is characterised by unrelenting nausea, recurrent vomiting, abdominal pain and compulsive, hot bathing behaviour. The symptoms contrast the traditional effects associated with cannabis use. We report a "textbook example" of a 26-year-old man with CHS. CHS is an important differential diagnosis to consider in patients with similar symptoms and the distinctive symptom relief in hot water. Early recognition may prevent extensive, unnecessary medical examinations and frequent hospital admissions.

2014 Nov Jehle et al looked at the rising trend of cannabis use in burn injury. Thousands of patients from the NBR (National Burn Repository) from 2002 to 2011were included. They found that the rate patients testing positive for cannabis in burn units is rising quickly. These patients are younger, less likely to be insured, have larger burns, spend more time in ICUs and have a greater number of operations.

2014 Andas et al detected the time taken for THC in oral fluid to disappear after frequent cannabis smoking. 26 drug addicts, admitted for detoxification in a closed detox unit were studied. Findings in oral fluid were compared with urine readings during monitored abstinence. THC was detected in 11 of the 26 patients. Negative samples could be interspersed with positive samples several days after cessation whereas THC-COOH concentrations in urine were decreasing. THC in this study was detected in oral fluid for up to 8 days after admission.

2014 Hunault et al investigated acute subjective effects after smoking joints containing up to 69mg Delta-9-THC (23% THC) in recreational users. 24 recreational users smoked joints of 4 potencies – placebo, 29, 49 and 69mg of THC on 4 separate test days in a randomised, double-blind, placebo-controlled study. Subjective effects were then measured after 8 hours on each occasion. The 'high' feeling, heart rate, blood pressure and THC serum concentrations were regularly recorded during the sessions. THC significantly increased the high feeling, dizziness, dry-mouthed feeling, palpitations, impaired memory and concentration, and 'down', 'sedated' and 'anxious' feelings. In addition, THC significantly decreased alertness, contentment and calmness. A cubic relationship was observed between 'feeling the drug' and 'wanting more'. The THC-induced decrease in 'feeling stimulated' and increase in anxiety lasted up to 8 h post-smoking. Sedation at 8 h post-smoking was increased by a factor of 5.7 with the highest THC dose, compared to the placebo.

They concluded that the study shows a strong effect of cannabis containing high percentages of THC on the rating of subjective effects. Regular users and forensic toxicologists should be aware that the THC-induced increase in 'feeling sedated' continues longer with a 69 mg THC dose than with a 29 mg THC dose.

2014 Kowal et al found that smoking cannabis does not make you more creative. Smokers who ingested a low dose of THC or none at all (they were given a placebo), performed best in thinking tasks. A high dose of THC was actually shown to have a negative effect on the ability to come up with as many solutions as possible to a problem. E.g. 'Think of as many uses you can for a pen' (divergent thinking) and 'finding the

only right answer to a problem – "What is the link between the words 'time', hair' and 'stretching'? The answer is 'long'.

2015 Koch et al explained the 'munchies' in a study at Yale. Cannabinoids hi-jack brain cells that normally suppress appetite. It suggests the cannabis causes the brain to produce a different set of chemicals that transform the feeling of fullness into a hunger that is never satisfied. Hovarth who led the study said, 'It's like pressing a car's brakes and accelerating instead'. A group of nerve cells (POMC pro-opiomelanocortin) neurons, which normally produces feelings of satiety, were activated to release hunger stimulating chemicals rather than appetite suppressing chemicals.

2015 Dzodzomenyo et al discovered that marijuana use is associated with excessive daytime sleepiness in adolescents. Ten per cent of adolescents sent to a Sleep Center for evaluation of excessive daytime sleepiness with testing results consistent with narcolepsy, confoundingly had urine drug screens positive for marijuana. This was a 10 year retrospective study of 383 children. 43% of children with positive urine tests for marijuana actually had test results consistent with narcolepsy or abnormal REM sleep patterns. Most didn't come back for repeat diagnostic studies after they were drug free.

29015 Feb Garcia-Morales et al looked at the acute use of cannabinoids and the depression of motor neuron activity. Synthetic analogues of the psychoactive compounds of marijuana significantly reduce the activity of motor neurons in animals – cannabinoids hinder the transmission of information so muscle weakness is produced. This could lead to problems speaking, breathing and even swallowing food, which would explain these difficulties suffered by some habitual users.

2015 Subbaraman and Kerr looked at people using cannabis and alcohol together and separately. Over 8,000 individuals were surveyed in this study. The results showed that the prevalence of simultaneous use was almost twice as high as concurrent use, implying that individuals who use both alcohol and cannabis tend to use them at the same time. Also simultaneous use was associated with increased frequency and quantity of alcohol use. Simultaneous use was also the most detrimental: compared to alcohol use only, simultaneous use approximately doubled the odds of drunk driving, social consequences, and harms to self, The magnitudes of differences in problems remained when comparing drunk driving among simultaneous users to concurrent users.

2015 April 30th, Murray wrote a general paper on marijuana, Marijuana and Madness: Clinical Implications of increased Availability and Potency. He updated the research findings on dependence, psychosis and cognitive impairment. He also highlighted the increased potency of skunk and the virtual absence of CBD.

2015 May, Hoch et al looked at the dark side of cannabis – panic attacks, nausea. Summary: Although the use of cannabis as a medical drug is booming, we should not forget that leisure time consumption – for example smoking weed - can cause acute and chronic harms. These include panic attacks, impaired coordination of movement and nausea . These symptoms depend on a person's age, the amount consumed and the frequency of drug use, also the form of cannabis used e.g. bong, joint or hash cake.

2015 Herrmann et al found that exposure to second-hand cannabis smoke causes mild intoxication. Second-hand exposure to cannabis smoke under 'extreme conditions (unventilated room or enclosed vehicle) can cause non-smokers to feel the effects of the drug, have minor problems with memory and coordination and in some cases test positive for the drug in urinalysis. Some participants did not pass the equivalent of a workplace drug test. The implications for driving need to be noted.

2015 Rizvi et al found that 'boys who smoke cannabis are 4 inches shorter'. Levels of puberty-related hormones such as testosterone and luteinizing hormone(LH), they discovered, were increased in cannabis smokers, and levels of the stress hormone cortisol were significantly higher. In contrast, growth hormone levels had decreased. Non-smoking boys were on average, four kilos heavier and 4.6 inches taller by the age of 20 than the dope smokers.

2015 May, Hartman et al found that any dose of alcohol combined with cannabis significantly increases the levels of THC and its primary active metabolite 11-hydroxy-THC(11-OH-THC), than cannabis use alone. In a study of motoer vehicle deaths, The US Dept of Transportation found an increased risk 0.7 for cannabis use, 7.4 for alcohol use and 8.4 for cannabis use and alcohol combined.

2015 Ogeil et al found that social drug users who report risky alcohol and cannabis use also report poor sleep. Women had poorer sleep outcomes than men. Problems with sleep quality were more common than complaints of excessive daytime sleepiness.

2015 May Fergusson et al, gave a research update – Psychosocial sequelae of cannabis use and implications for policy: findings from The Christchurch Health and Development Study. In general, the findings of the CHDS suggest that individuals who use cannabis regularly, or who begin using cannabis at earlier ages, are

at increased risk of a range of adverse outcomes, including: lower levels of educational attainment; welfare dependence and unemployment; using other, more dangerous illicit drugs; and psychotic symptomatology. It should also be noted, however, that there is a substantial proportion of regular adult users who do not experience harmful consequences as a result of cannabis use. They concluded: Collectively, these findings suggest that cannabis policy needs to be further developed and evaluated in order to find the best way to regulate a widely-used, and increasingly legal substance.

2015 May, Bui et al report on a case of marijuana intoxication. We use a case report to describe the acute psychiatric and medical management of marijuana intoxication in the emergency setting. A 34-year-old woman presented with erratic, disruptive behavior and psychotic symptoms after recreational ingestion of edible cannabis. She was also found to have mild hypokalemia and QT interval prolongation. Psychiatric management of cannabis psychosis involves symptomatic treatment and maintenance of safety during detoxification. Acute medical complications of marijuana use are primarily cardiovascular and respiratory in nature; electrolyte and electrocardiogram monitoring is indicated. This patient's psychosis, hypokalemia and prolonged QTc interval resolved over two days with supportive treatment and minimal intervention in the emergency department. Patients with cannabis psychosis are at risk for further psychotic sequelae. Emergency providers may reduce this risk through appropriate diagnosis, acute treatment, and referral for outpatient care.

2015 May, Lee et al Looked at unemployment predictions among marijuana users. Six hundred seventy-four participants (53% African-Americans, 47% Puerto Ricans) were surveyed (60% females) from ages 14 to 36. The first data collection was held when the participants were students attending schools in the East Harlem area of New York City. We found that the chronic marijuana use and the late marijuana quitter trajectory groups were associated with an increased likelihood of unemployment compared with the no marijuana use trajectory group. The results suggest that those who use marijuana chronically are at greater risk for being unemployed.

2015 May, Keith and others looked at undergraduates at one university in the USA. Approximately 1 in 12 undergraduates (8.5%) reported using marijuana more than 10 days in the past month. Frequent marijuana use was associated with increased likelihood of other substance use and alcohol-related negative outcomes. Marijuana use was associated with increased reports of anxiety, and frequent use was associated with depression and substance use problems. Perceived stress was not associated with marijuana use.

2015 Onders et al reported on marijuana exposure among children under 6 in the USA. Marijuana exposure among children of 5 and younger rose 147% from 2006- 2013 across the USA. In states where it has been legalised for medical use before 2000, the rise was 610%. More than 75% of the exposed children were under 3, and most had swallowed marijuana. Most cases resulted in only minor clinical effects but some experienced coma, decreased breathing or seizures. More than 18% were hospitalised. Overall there were 1969 young children reported to The Poison Control Centres in the USA for marijuana exposure between 2000 and 2013.

2015 June Kim et al looked at cyclic vomiting presentations following marijuana liberization in Colorado. The prevalence of cyclic vomiting increased from 41 per 113,262 ED visits to 87 per 125,095 visits after marijuana legalisation – almost double the numbers. Patients in the postliberization period were more likely to endorse marijuana use.

2015 USA. Thompson et al looked at the prevalence of marijuana-related traffic on Twitter, 2012-3. 36969 original tweets were analysed. A majority from adolescents (65.6%) reflected a positive attitude towards cannabis 42% indicating personal use. 36.0% indicated parental support for the adolescent's use. Adolescents and others on Twitter are being exposed to positive discussion, normalising use. Twitter was increasingly used to disclose marijuana use.

2015 Whiting et al undertook a systematic review and meta-analysis of cannabinoids for medical use. 79 trials were included. There was moderate quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders and Tourette Syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

2015 Hasin et al looked at medical marijuana laws and adolescent use in the USA from 1991 to 2014. Data was obtained from The Monitoring The Future Study. Around 400 schools are involved looking at 8th, 10th and 12th grade students. Any marijuana used in the past 30 days was monitored. They concluded that 'overall, adolescent use is higher in states that ever passed such a law than in other states but the passing of state marijuana laws does not seem to increase the use of marijuana.

2015 Miech and others looked at the trends in use of marijuana and attitudes towards marijuana among youth before and after decriminalisation: The case for California 2007-2013. Data from The Monitoring The Future was used to investigate 8th, 10th and 12th grade students. In 2012 and afterwards, as compared to their peers in other states, California 12th graders were 25% more likely to have used marijuana in the last 30 days, 20% less likely to perceive regular marijuana use as a great health risk, and 20% less likely to strongly disapprove of regular marijuana use, and about 0% morelikely to expect to be using marijuana five years in the future.

2015 Dube et al looked at weight gain in cannabis users. It is well known that cannabis stimulates the appetite but less is known about possible weight gain. 1294 young people aged 12 or 13 agreed to share information about their daily lives. It was found that cannabis use does indeed influence weight gain but various other factors modify the effects. In male non-cigarette smokers, greater cannabis use increased weight, while in cigarette smokers, the effect was almost the opposite. THC and nicotine affect males and females differently, hormonal changes and possible psychological differences may be involved. Frequency of use and general activity were other factors.

2015 D'Amico et al Looked at medical marijuana adverts and their influence on children. Sixth to eighth grade youth, 8214 in 16 middle schools in South California were surveyed (average age 13). Exposure to advertising for medical marijuana, marijuana intentions and marijuana use were assessed. Greater initial medical marijuana advertising exposure was significantly associated with a high probability of marijuana use and stronger intentions to use a year later, and initial marijuana use and stronger intentions to use were associated with greater medical marijuana advertising exposure a year later.

2015 Mair et al Looked at places with more marijuana dispensaries and hospitalizations. When the location of marijuana dispensaries were mapped and cross-referenced it with the ZIP code of each patient's home, they found that each additional dispensary per square mile in a ZIP code was associated with a 6.8% increase in the number of hospitalizations linked to marijuana abuse and dependence.

2015 Kosty et al looked at parental transmission of risk for cannabis use disorders to offspring. 719 probands were studied along with their biological mothers and fathers. There was an increased risk for CUD onset among probands with parental histories of CUD, hard drug use disorders or antisocial personality disorder. Females with a maternal CUD history were at higher risk for CUD onset compared with females without a maternal CUD. Maternal CUD was not associated with CUD onset among males, nor was there evidence for parent-offspring gender concordance for paternal effects for paternal CUD-specific transmission.

2015 Hancock-Allen et al looked at a death following ingestion of an edible marijuana product. A 23 year old had purchased marijuana cookies and gave one to his 19 year old friend. Contrary to instructions he ate the whole cookie. For the next 2 hours, he exhibited hostile behaviour and erratic speech. He then jumped off a fourth floor balcony and died from trauma. Marijuana intoxication was found to be the chief contributing factor. No other drug was present.

2015 Liakoni et al reported on acute health problems due to recreational drug use at an urban emergency department in Switzerland. All cases between October 2013 and September 2014 were examined. 216 cases were directly related to acute toxicity of recreational drugs – mean age 31, and 69% were male. Cocaine was most common (36%) followed by cannabis (31%). They concluded, 'Medical problems related to illicit use of drugs mostly concerned cocaine and cannabis and mainly involved sympathomimetic toxicity and/or psychiatric disorders.

2015 Lu and Agito found that marijuana is both anti-emetic and pro-emetic. Although marijuana is sometimes used to treat chemotherapy-induced nausea and vomiting, when used long-term it can have a paradoxical hyperemetic effect known as cannabinoid hyperemesis syndrome. Knowledge of this phenomenon may reduce the ordering of unnecessary and expensive investigations, as well as inappropriate medical and surgical treatment in patients presenting with recurrent vomiting of unknown cause. This article reviews the pathophysiology, clinical presentation, diagnosis, and management of this emerging condition.

2015 Decuyper et al addressed cannabis allergy. For about a decade, IgE-mediated cannabis (marihuana) allergy seems to be on the rise. Both active and passive exposure to cannabis allergens may lead to a cannabis sensitization and/or allergy. The clinical manifestations of a cannabis allergy can vary from mild to life-threatening reactions, often depending on the route of exposure. In addition, sensitization to cannabis allergens can trigger various secondary cross-allergies, mostly for plant-derived food. This clinical entity, which we have designated as the "cannabis-fruit/vegetable syndrome" might also imply cross-reactivity with tobacco, latex and plant-food derived alcoholic beverages. These secondary cross-allergies are mainly described in Europe and appear to result from cross-reactivity between non-specific lipid transfer proteins

or thaumatin-like proteins present in Cannabis sativa and their homologues that are ubiquitously distributed throughout plant kingdom. At present, diagnosis of cannabis-related allergies rests upon a thorough history completed with skin testing using native extracts from buds and leaves. However, quantification of specific IgE antibodies and basophil activation tests can also be helpful to establish correct diagnosis. In the absence of a cure, treatment comprises absolute avoidance measures including a stop of any further cannabis (ab)use.

2015 Danielsson et al studied the use of cannabis and the risk of adverse life course outcomes. A total of 49 321 Swedish men born in 1949-51, who were conscripted to compulsory military service at 18-20 years of age were studied. Individuals who used cannabis at high levels in adolescence had increased risk of future unemployment and of receiving social welfare assistance. Adjusted for all confounders (social background, psychological functioning, health behaviours, educational level, psychiatric diagnoses), an increased relative risk of unemployment and social welfare assisance remained in the group reporting cannabis use > 50 times.

2015 Salas-Wright et al investigated trends in disapproval and use of marijuana in the US 2002-2013. Between 2002 and 2013 the proportion of adolescents aged 12-14 reporting "strong disapproval" of marijuana use initiation increased significantly from 74.4-78.9%. Concurrently, a significant decrease in past 12-month marijuana use was observed among younger adolescents. No significant trend was observed for marijuana use disapproval among adolescents aged 15-17 between 2002 and 2013. Yet a significant decrease in the past 12-month marijuana use was observed (2002 = 26.2%, 2013 = 21.9%) among this group. Among young adults (aged 18-25), a substantial decrease - from 40.5% in 2002 to 22.6% in 2013 - was observed in the proportion reporting "strong disapproval" of marijuana use initiation; however, increases in the past 12-month use were relatively small among young adults but statistically significant.

2015 Cone et al looked at passive smoking. The increasing use of highly potent strains of cannabis prompted this new evaluation of human toxicology and subjective effects following passive exposure to cannabis smoke. The study was designed to produce extreme cannabis smoke exposure conditions tolerable to drug-free nonsmokers. Six experienced cannabis users smoked cannabis cigarettes [5.3% Δ(9)-tetrahydrocannabinol (THC) in Session 1 and 11.3% THC in Sessions 2 and 3] in a closed chamber. Six non-smokers were seated alternately with smokers during exposure sessions of 1 h duration. Sessions 1 and 2 were conducted with no ventilation and ventilation was employed in Session 3. Positive tests for THC in oral fluid and blood were obtained for non-smokers up to 3 h following exposure. Ratings of subjective effects correlated with the degree of exposure. Subjective effect measures and amounts of THC absorbed by non-smokers (relative to smokers) indicated that extreme second-hand cannabis smoke exposure mimicked, though to a lesser extent, active cannabis smoking.

2015 Wen et al looked at the effects of medical marijuana laws on adolescent and adult use of marijuana, alcohol and other substances. The effect of medical marijuana laws (MMLs) in ten states between 2004 and 2012 on adolescent and adult use of marijuana, alcohol, and other psychoactive substances was estimated. Increases in the probability of current marijuana use, regular marijuana use and marijuana abuse/dependence among those aged 21 or above were found. There was also an increase in marijuana use initiation among those aged 12-20. For those aged 21 or above, MMLs further increase the frequency of binge drinking. MMLs have no discernible impact on drinking behavior for those aged 12-20, or the use of other psychoactive substances in either age group.

2015 Driedger et al looked at what kids are getting up to – presentations to a Canadian pediatric emergency department. They conducted a retrospective review of all youth, ages 10-16 years, who presented to a pediatric ED with complaints related to recreational drug use (n=641) for 2 years ending on December 31, 2009. The median age of patients was 15 years; 56% were female. Six percent of patients were homeless, and 21% were wards of the state. The most frequent ingestions included ethanol (74%), marijuana (20%), ecstasy (19%), and medications (15%). Over one third of patients had ingested two or more substances. Sixty-eight percent received IV fluids, 42% received medication and 4% were intubated. The admission rate was 9%.

2015 Boyd et al looked at the use of medical marijuana by adolescents. They wanted to examine the annual use of medical marijuana and determine if legal medical marijuana users are at lower risk for frequent marijuana and other substance use when compared to adolescents who use diverted medical marijuanaor from an illicit source. 4394 12^{th} graders were studied. Users of medical marijuana and diverted medical marijuana had notable odds of using daily, using prescription drugs, and using other illicit drugs among other substance use behaviours. Medical marijuana users had much higher odds of using medical marijuana because of being hooked when compared to diverted medical users and illicit users.

2015 Freisthler et al investigated the relationship between Marijuana use, medical marijuana dispensaries and abusive and neglectful parenting. Current marijuana use was positively related to frequency of child physical abuse and negatively related to physical neglect. There was no relationship between supervisory neglect and marijuana use. Density of medical marijuana dispensaries and delivery services was positively related to frequency of physical abuse.

2015 Lanza et al reported that alcohol use is declining among teens but marijuana use is on the rise. Survey results from almost 600,000 American high school seniors between 1976 and 2013, alcohol, cigarettes and marijuana use were monitored. In 1993 black teenagers were equally likely to use tobacco and marijuana, and have continued an upward trend in marijuana use since. White adolescents were more likely to smoke cigarettes than use marijuana until 2011, when marijuana use slightly surpassed that of cigarettes. In 2013, nearly 19% of white teens smoked cigarettes while almost 22% used marijuana. At the same time, only about 10% of black teens smoked cigarettes but nearly 25% used marijuana.

2015 Weitzman et al found many teens with chronic illnesses (e.g. asthma, juvenile arthritis, type 1 diabetes, cystic fibrosis) use pot and/or alcohol. Four out of ten high school students with medical conditions used one or both in the past year. Just over 400 students (age 9-18) were studied, average age 15. 75% were white and almost 75% had a parent with a college degree. Most of them (82%) were in high school. More than a third had consumed alcohol in the last year, a fifth had used marijuana in the last 12 months. Those taking alcohol were more likely to have missed taking their medication. Most had no idea of any interactions with alcohol or marijuana and their medication.

2015 Ruffle et al looked at cannabinoid hyperemesis syndrome (CHS). CHS is often undiagnosed and treated as cyclic vomiting syndrome, a functional gastrointestinal problem. Data from 2013-2015 was studied. 10 cases of CHS in men had been misdiagnosed. The mean length of cannabis use was 42 months. Healthcare providers should be aware of this and questions about cannabis use should be asked.

2015 Kaar et al in Australia investigated trends in cannabis-related ambulance presentations from 2000 to 2013. Rates of cannabis-related ambulance attendances involving 15-59 year olds were studied. The rates increased significantly over the period. In 2000-2010 the rate/100,000 was 0.6 to 5.5 in 2010-2013. The highest increasing rate (15.6) was for Cannabis-Only attendances among 15-29 year old males.

2015 Krauss et al looked at marijuana dabbing videos on YouTube. 116 videos were found. Total views were 9,545,482. Most were located in California. 89% showed at least one person dabbing, most were male (67%), many (42%0 appeared to be under 25 years old. Only 20% had an age restriction Approximately 34% contained a product review, 28% provided instructions on dabbing or other educational information. 21% contained at least a brief cautionary message.

2015 Daniulaityte et al Looked at Twitter data on dabs. 125,255 tweets were collected between October 20th and December 20th 2014. Almost 22% contained identifiable state-location geological information. Dab-related tweets were highest in states that allowed recereational and/or medical use. And lowest in states that have not passed medical laws. Results were statistically significant.

2015 Vaughn et al Investigated home-schooled adolescents and whether they were less likely to use alcohol, tobacco and other drugs? In the US nearly 2million children are home-schooled. Data between 2002 and 2013 from the National Survey on Drug Use and Health were used. Home-schooled adolescents were significantly less likely to report using tobacco, alcohol, cannabis or other illicit drugs, and to be diagnosed with an alcohol or marijuana use disorder.

2015 Parker and Bradshaw investigated teen dating violence (TVD) victimisation and patterns of substance use among high school students. The adolescents who had experienced physical and psychological TVD were more likely to be polysubstance users or use alcohol and marijuana.

2015 Bancks et al looked at 3,000 people in America and found that people who currently used marijuana were 65% more likely to have poor sugar control which can lead to type 2 diabetes. Those who had smoked it 100 times or more but no longer used, were 49% more likely. A heightened incidence of pre-diabetes failed to establish a direct connection to diabetes 2 itself, however it is unclear how marijuana could place someone at increased risk for pre-diabetes and not diabetes itself.

2015 Kleine-Brueggeney et al looked at medical marijuana (THC extract) to prevent nausea and vomiting after surgery in patients at high risk of this common complication (gynaecological or breast surgery). Intravenous THC or a placebo were administered before surgery was completed. 300 patients were assigned to the study but the the trial was halted after the first 40 patients due to 'clinically unacceptable' side-effects of THC as well as questionable effects on post-operative nausea and vomiting (PONV). In both THC and placebo groups, about 60-70% of patients experienced PONV during the first 24 hours. The relative risk reduction of THC was just 12% - well under the statistically significant cut off point. Problems with side-effects included: THC patients were more sedated, psychotrophic effects (mood changes) were 'unpredictable in quality and quantity, patient satisfaction varied from 'best experience' to 'the worst ever'.

2015 Wei and others tested for secondhand marijuana exposure with a very sensitive urine test. They cmbined ultra high performance liquid chromatography and tandem mass spectrometry with positive electro-spray ionization mode to develop a reliable fast and accurate method to test for THC and its metabolites (10-100 times more sensitive than current tests).

2015 Hasin and others reported the prevalence of marijuana use disorders in US adults between 2001-2 and 2012-3. The past year, prevalence of marijuana use was 4.1% in 2001-2 and 9.5% in 2012-3. The past year prevanence of DSM-IV marijuana use disorder was 1.5% in 2001-2 and 2.9% in 2012-3.

2015 Deogan et al looked at the cost-effectiveness of school-based prevention of cannabis use. The cost-effectiveness of Project ALERT (Adolescent, Learning, Experiences, Resistance and Training) compared with the ordinary ATOD (Alcohol, Tobacco and Other Drug Education) among Swedish students in the eigth grade of compulsory school. The programme was cost saving on the basis of evidence from the USA (ratio 1:1.1), and was cost effective (incremental cost-effectiveness ratio €22,384 per QALY) after reasonable adjustment for the Swedish context and with 20 years of follow-up. When the target group was restricted to boys who were neither studying nor working/doing work experience, the programme was cost effective after 9 years and cost saving (ratio 1:3.2) after 20 years.

2015 Fitzcharles et al looked at cannabinoid treatments in rheumatic diseases. In four short-term studies comprising 201 patients, cannabinoids had a statistically significant effect on pain in 2 of them, sleep in two and improved quality of life in one. The study in OA was terminated prematurely due to futility. Dizziness, cognitive problems and drowsiness as well as nausea were reported for nearly half the patients. No serious adverse effects, no studies done with herbal cannabis. Conclusion: There is currently insufficient evidence to recommend cannabinoid treatments for management of rheumatic diseases.

2015 Lavi et al reported on sudden onset unexplained encephalopathy in infants. Three infants presented to an emergency department with encephalopathic signs without prominent systemic manifestations. There was no information about neurotoxic agents available. All three were subsequently diagnosed with THC intoxication. All three recovered with supportive care, fluids and monitoring. The importance of including cannabis intoxication in the differential diagnosis of infants with unexplained changes in mental status.

2015 Bell et al looked at hash oil burns in Colorado. 29 cases were admitted to the local burn center from January 2008 to August 2014 (utilizing the National Burns Repository). No cases presented prior to the medicalization of marijuana, 19 during this time and 12 in 2014 since legalization. The majority were white Caucasians, average age 26. Median range of stay was 10 days. 6 required intubation (airway protection), 19 skin grafts, 8 wound care only and one surgical debridement.

2015 Madras BK of Harvard Medical School published an 'Update of Cannabis and its Medical Use'. It included the chemistry of cannabis, signalling in the brain, toxicity, abuse, CUDs (Cannabis Use Disorders) and use in medicine.

2015 Dines AM, Wood DM, Galicia M, Yates CM, Heyerdahl F, Hovda KE, Giraudon I, Sedefov R; Euro-DEN Research Group, Dargan PI. Presentations to the Emergency Department Following Cannabis use-a Multi-Centre Case Series from Ten European Countries. J Med Toxicol. 2015 Dec;11(4):415-21. doi: 10.1007/s13181-014-0460-x.

2015 Pacula et al produced 'In the weeds': a baseline view of cannabis use among legalising states and their neighbours. Individuals, 2009 from Washington, Oregon 506, Colorado 503 and New Mexico 213 were involved. Mean age was 53 (18-91).

Results "Rates of lifetime medical cannabis use are similar in Colorado and Washington (8°8% and 8°2%) but lower in Oregon and New Mexico (6.5% and 1%). Recreational use is considerably higher than medical use across all states (41%) but highest in Oregon and Washington. About 86% of people who report ever

using cannabis for medicinal purposes also use it recreationally. Medical users are more likely to vaporize and consume edibles, and report a higher amount (in grams) consumed, and spend more money per month than recreational users. Individuals who use cannabis do not commonly use it with alcohol, irrespective of whether they are consuming cannabis recreationally or medically. Fewer than 1 in 5 recreational users report simultaneous use of alcohol and cannabis most or all of the time and less than 3% of medicinal users report frequent simultaneous use of alcohol and cannabis".

They concluded "In the USA, the degree of overlap between medicinal and recreational cannabis users is 86%. Medicinal and recreational cannabis users favour different modes and amounts of consumption. Only a small proportion (12%) of medicinal cannabis users usually consume cannabis and alcohol simultaneously, while concurrent use is common among recreational users".

2015 Morean et al looked at the use of e-cigarettes to vaporize cannabis. They evaluated lifetime rates of using e-cigarettes to vaporize cannabis among, lifetime users of e-cigarettes (27.9%), lifetime users of cannabis (29.2%) and lifetime users of both e-cigs and cannabis(18.8%). It proved to be common in all groups, to vaporize hash oil, wax infused with THC, and dried cannabis leaves.

2015 Scholes-Balog et al examined adolescent cannabis users and their relationship to adult social and behavioural adjustment. Participants, 852 (female 53%) were part of The International Youth Development Study, average age 21. Trajectories of cannabis use frequency were used from average age 12 to average age 19. Three trajectories were identified, abstainers (62%), early onset users (11%) and late onset occasional users (27%). 'The early onset users showed a higher frequency of antisocial behaviour, violence, cannabis use, cannabis-related harms, cigarette use, and alcohol harms, compared to the abstinent group in young adulthood. The late onset occasional users reported a higher frequency of cannabis use, cannabis-related harms, illicit drug use, and alcohol harms, compared to the abstinent group in young adulthood. There were no differences between the trajectory groups on measures of employment, school completion, post-secondary education, income, depression/anxiety, or alcohol use problems. In conclusion, early onset of cannabis use, even at relatively low frequency during adolescence, is associated with poorer adjustment in young adulthood'.

2015 Ocampo and Rans wrote a paper on cannabis allergy. Conclusions Although still relatively uncommon, allergic disease associated with *C sativa* exposure and use has been reported with increased frequency. Allergic reactions and even anaphylaxis attributed to *C sativa* have been noted with sensitization associated with pollinosis, *Cannabis* use, potential plant cross-reactivity, and occupational exposure. With state laws allowing medical and in some cases recreational use of marijuana, there is a growing potential for legitimate personal and commercial exposure. The evolving legal status of *C sativa*, its highly prevalent use throughout the world, and the varied forms in which it is used could translate into its growing role as a clinically relevant allergen that might be encountered.

Crude extracts have been used in different in vivo and in vitro testing methods to demonstrate the immunologic nature of these cases. However, the lack of standardized extracts limits validation and widespread applicability of such diagnostic testing. Much research is still needed to more definitively define pertinent allergens, develop a standardized extract, establish diagnostic sensitivity and specificity, and clarify treatment options for clinically affected *Cannabis*-allergic patients.

2016 Marijuana wax (Honey oil, shatter, dabs) Marijuana wax is not marijuana, there is an extremely bad hallucinatory side. You can overdose on concentrates though it isn't fatal. To make the drug, butane and other chemicals are used to draw out THC from marijuana plants. Wax can have a potency of up to 95 percent. Police have responded to calls for people who were "far beyond high and debilitated" on wax. It's the meth of the marijuana world. The popularity of the drug has soared in recent years due to its increased potency, lack of odour and ease of concealment – the drug can be loaded into E-cigarettes and smoked through vaporizers. Wax could be 20 to 30 times more potent than regular marijuana.

2016 January Russo was interviewd by the Jouurnal Cannabis and Cannabinoid Research (Dr Piomelli) about Cannabis sativa v Cannabis indica. Apart from THC, cannabinol and cannabidiol, there are many additional components that may increase or modify their effects, e.g. terpenes such as myrcene a strong sedative and alpha-pinene that may counteract the tendency of THC to impair short-term memory. Dr Russo argues that while the C. sativa and C. indica strains are morphologically different, the common notion that C. sativa is 'uplifting and energetic' while C. indica is sedating is completely wrong. 'Almost all Cannabis on the market has been from high-THC strains. The differences in observed effects in Cannabis are then due to their terpenoid content, rarely assayed, let alone reported to potential customers. The sedation of the so-called indica strains is falsely attributed to CBD content, when in fact, CBD is stimulating in low and moderate doses'.

2016 Weinberger et al found that marijuana users were 5 times more likely to develop an alcohol use disorder, alcohol abuse or dependency. The researchers analyzed data from 27,461 adults enrolled in the National Epidemiologic Survey on Alcohol and Related Conditions who first used marijuana at a time when they had no lifetime history of alcohol use disorders. The population was assessed at two time points. Adults who had used marijuana at the first assessment and again over the following three years (23 percent) were five times more likely to develop an alcohol use problem, compared with those who had not used marijuana (5 percent). Adult problem drinkers who did not use cannabis were significantly more likely to be in recovery from alcohol use disorders three years later.

2016 Volkow et al conducted a review of the effects of cannabis on human behaviour. With a political debate about the potential risks and benefits of cannabis use as a backdrop, the wave of legalization and liberalization initiatives continues to spread. Four states (Colorado, Washington, Oregon, and Alaska) and the District of Columbia have passed laws that legalized cannabis for recreational use by adults, and 23 others plus the District of Columbia now regulate cannabis use for medical purposes. These policy changes could trigger a broad range of unintended consequences, with profound and lasting implications for the health and social systems in our country. Cannabis use is emerging as one among many interacting factors that can affect brain development and mental function. To inform the political discourse with scientific evidence, the literature was reviewed to identify what is known and not known about the effects of cannabis use on human behavior, including cognition, motivation, and psychosis.

2016. Troup et al looked at the effects of cannabis on emotion processing. Cannabis users showed a greater response to faces showing negative expressions, especially angry faces, compared to a control group of non-cannabis users. Positive expressions, e.g. happy faces elicited smaller responses. When asked to concentrate on the sex of the face and then identify the emotion, cannabis users scored much lower than non-users. There was a depressed ability to 'implicitly' identify emotions.

2016 Cerda et al looked at persistent cannabis and alcohol dependence and midlife economic and social risks. Summary of Findings: 'People who smoked cannabis four or more days of the week over many years ended up in a lower social class than their parents, with lower-paying, less skilled and less prestigious jobs than those who were not regular cannabis smokers, shows a research study that followed children from birth up to age 38. These regular and persistent users also experienced more financial, work-related and relationship difficulties, which worsened as the number of years of regular cannabis use progressed'. Caspi said, '"These findings did not arise because cannabis users were prosecuted and had a criminal record, even among cannabis users who were never convicted for a cannabis offense, we found that persistent and regular cannabis use was linked to economic and social problems." Findings came from The Dunedin Study.

2016 Patsenker et al reviewed cannabinoids in liver disease. ' Mounting evidence indicates that the ECS (Endocannabinoid System) plays an important role in various liver diseases including viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, hepatic encephalopathy, and auto-immune hepatitis. The ECS also impacts on involved processes such as hepatitis hemodynamics, nutrient intake and turnover, and ischemia reperfusion (VR) after liver transplantation. Although this involvement is undisputed, therapeutic implications regarding the ECS are just beginning to emerge; so far, no approved drug acting specifically on the ECS is available'.

2016 Miller et al Looked at group identifications and how they affect the likelihood of teenagers smoking, drinking and taking cannabis. Summary 'Teenagers who interact positively with their family, school and friends are far less likely to smoke, binge drink and use cannabis than peers who fail to identify with these social groups, according to research. The research team surveyed more than 1000 high school pupils aged 13-17 from the Fife area. The results showed that group identification protects against adverse health behavior, with levels of identification with family, school and friendship groups predicting the likelihood of teenagers having smoked cigarettes, drank to excess or smoked cannabis in the past month'.

2016 Hashmi et al reported a case of cannabis-induced hemoptysis in a cannabis smoker. Abstract: 'Abstract: As the principal route of marijuana use is by inhalation, potential harmful consequences on pulmonary structure and function can be anticipated. Here, we present a case of hemoptysis attributed to smoking cannabis in a 38-year-old man. The patient experienced an episode of hemoptysis and shortness of breath immediately after smoking marijuana. Chest radiograph and computed tomography (CT) scans of the chest showed bilateral diffuse ground-glass opacities. A

fiber optic bronchoscopy confirmed bilateral diffuse bleeding from respiratory tract. Additional evaluation of hemoptysis indicated no infection or immunological responses. Urine toxicology was positive for cannabis'.

2016 Davis et al looked at The public Health Effects of Medical Marijuana legalisation in Colorado. Data from Denver metropolitan area and Colorado were collected for hospital discharges and poison centre calls before and after 2009 and analysed in 2014. Hospital discharges coded as marijuana dependent rose by 1% every month from 2007 to 2013. After 2009, poison center calls increasedby 0.8%/month. Poison Center calls also increased 56% in the period following the policy change. There was one hospital discharge coded as dependent for every 3,159 medical marijuana registrant applications.

2016 International cannabis consortium, Stringer et al aims to identify genetic risk variants of cannabis use. Four genes were found to be significantly associated with lifetime cannabis use – NCAM1, CADM2, SCOC and KCNT2. There is a strong genetic correlation between lifetime cannabis use and cigarette smoking.

2016 Olsson and others looked at risk factors for untimely deaths, using a register follow-up in a criminal justice population with substance use problems. They found that fatal accidental intoxication was associated with males, use of heroin and use of cannabis.

2016 Zhang et al looked at marijuana use as a predictor of unemployment status in the early forties. 'Five trajectories of marijuana use were identified: chronic users/decreasers (8.3%), quitters (18.6%), increasing users (7.3%), chronic occasional users (25.6%), and nonusers/experimenters (40.2%). Compared with nonusers/experimenters, chronic users/decreasers had a significantly higher likelihood of unemployment at mean age 43 (adjusted odds ratio = 3.51), even after controlling for the covariates'.

2016 Desjardins et al reviewed the litersture concerning cannabinoid hyperemesis syndrome. Abstract: 'Cannabis is the most widely used illicit drug in the world. In France, cannabis use has been increasing among youth since 2011, in both experimental use and regular consumption. A distinct syndrome, characterized by recurrent vomiting associated with abdominal pain and compulsive bathing, has been increasingly recognized in adult chronic users. Cannabinoid hyperemesis syndrome (CHS) is still underdiagnosed in adults and even more so among adolescents. Classically, CHS progresses into three distinct phases: prodromal, hyperemetic, and recovery. During the prodromal phase, the patient develops early morning nausea, a fear of vomiting, and abdominal discomfort. Afterward, the hyperemetic phase consists of incapacitating nausea and profuse vomiting. Most patients complain of mild abdominal pain and weight loss. Patients are relieved by taking hot showers. The recovery stage begins with cessation of cannabis use. The majority of patients will develop this symptom within 1-5years after the beginning of consumption. CHS is a clinical diagnosis and should be considered in every case of cyclical vomiting. To date, the specific etiology of CHS is unknown as is the pathophysiology of improvement with hot baths. All youth presenting with cyclic vomiting should be questioned about cannabis use and compulsive hot bathing. The early recognition of this syndrome will save unnecessary and invasive investigations'.

2016 van de Giessen et al investigated deficits in striatal dopamine release in cannabis dependence. Most drugs of abuse lead to a general blunting of dopamine release in the chronic phase of dependence, which contributes to poor outcome. To test whether cannabis dependence is associated with a similar dopaminergic deficit, we examined striatal and extrastriatal dopamine release in severely cannabis-dependent participants (CD), free of any comorbid conditions, including nicotine use. Lower dopamine release in the associative striatum correlated with inattention and negative symptoms in Cannabis Dependents, and with poorer working memory and probabilistic category learning performance in both CD and Healthy Controls. This study provides evidence that severe cannabis dependence-without the confounds of any comorbidity-is associated with a deficit in striatal dopamine release. This deficit extends to other extrastriatal areas and predicts subclinical psychopathology.

2016 Manrique-Garcia et al looked at cannabis, psychosis and mortality in a cohort study of 50,373 men. A longitudinal study of 50,373 Swedish male conscripts aged 18-19 followed in the National Cause of Death Register up to around age 60. Those with a baseline history of heavy cannabis use had a significantly higher risk of death than those without such a history they were 40% more likely to die around the age of 60 than non-users. No interaction was found between cannabis use and a diagnosis of psychotic disorders with regard to mortality.

2016 Wilson et al found that 1 in 6 children hospitalized (Colorado hospital) for lung inflammation (coughing, wheezing and other symptoms of bronchiolitis) tested positive for marijuana exposure. More of the children were positive for THC after legalisation (21% compared with 10% before). Secondhand smoke may be a rising child health concern.

2016 Rosevear reported urological problems in his practice in Colorado. Two men after having vasectomies reported experiencing a seizure. They had both used cannabis. A young couple in their twenties reported infertility after a year. The male's sperm showed abnormal morphology, decreased counts and low motility. Again they both confessed to using cannabis, almost daily. A few months later, after abstaining, she conceived.

2016 Ramaekers et al looked at Cannabis and tolerance and acute drug impairment as a function of cannabis use history.

Abstract: Cannabis use history as predictor of neurocognitive response to cannabis intoxication remains subject to scientific and policy debates. The present study assessed the influence of cannabis on neurocognition in cannabis users whose cannabis use history ranged from infrequent to daily use. Drug users (N = 122) received acute doses of cannabis (300 μg/kg THC), cocaine HCl (300 mg) and placebo. Cocaine served as active control for demonstrating neurocognitive test sensitivity. Executive function, impulse control, attention, psychomotor function and subjective intoxication were significantly worse after cannabis administration relative to placebo. Cocaine improved psychomotor function and attention, impaired impulse control and increased feelings of intoxication. Acute effects of cannabis and cocaine on neurocognitive performance were similar across cannabis users irrespective of their cannabis use history. Absence of tolerance implies that that frequent cannabis use and intoxication can be expected to interfere with neurocognitive performance in many daily environments such as school, work or traffic.

2016 Reece et Hulse looked at Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity 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.

2016 Meier et al looked at results from The Dunedin study, now 38 years old, and the associations between cannabis use and physical health problems in early midlife.
They tested whether cannabis use from ages 18 to 38 years was associated with physical health at age 38, after controlling for tobacco use, childhood health, and childhood socioeconomic status. They also tested whether cannabis use from ages 26 to 38 years was associated with within-individual health decline using the same measures of health at both ages. Frequency of cannabis use and cannabis dependence at ages 18, 21, 26, 32, and 38 years was tested.
The 1037 study participants were 51.6% male (n = 535). Of these, 484 had ever used tobacco daily and 675 had ever used cannabis. Cannabis use was associated with poorer periodontal health at age 38 years and within-individual decline in periodontal health from ages 26 to 38 years. For example, cannabis joint-years from ages 18 to 38 years was associated with poorer periodontal health at age 38 years, even after controlling for tobacco pack-years. Additionally, cannabis joint-years from ages 26 to 38 years was

associated with poorer periodontal health at age 38 years, even after accounting for periodontal health at age 26 years and tobacco pack-years. However, cannabis use was unrelated to other physical health problems. Unlike cannabis use, tobacco use was associated with worse lung function, systemic inflammation, and metabolic health at age 38 years, as well as within-individual decline in health from ages 26 to 38 years.

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2016 Hindocha et al investigated whether the combination of tobacco and cannabis can increase the likelihood of dependence. 33,687 cannabis users, participants of the 2014 Global Drug Survey, took part anonymously in the research. Tobacco routes for cannabis, joints, blunts or pipes are most popular in Europe (between 77.2% and 90.9%) while only 51.6% of Australians and 20.7% of New Zealanders used them. They are least popular in the Americas. Cannabis users who favour non-tobacco routes had 61.5% higher odds of wanting professional help to use less cannabis and 80.6% higher odds of wanting to use less tobacco than those who used tobacco routes. Cannabis users who prefer non-tobacco routes had 10.7% higher odds of wanting to use lss tobacco and 103.9% higher odds of actively planning to seek help to use less tobacco. These results suggest that people who regularly mix tobacco with cannabis are more at risk of psychological dependence than those who use cannabis and tobacco separately, without mixing them.

2016 Chen et al looked at current patterns of marijuana use initiation by age among US adolescents and emerging adults. 26,659 participants ages 12 to 21 from the National Survey on Drug Use and Health, 54.4% male, 55.6% white) were analysed. Up to age 11 the hazards were small but did occur. After age 11 the hazards increased rapidly with two peaks at 16 and 18, separated by a reduction at 17. The age pattern differed significantly by gender, hazards high to low, male to female and race/ethnicity hazards high to low – multiracial, Black, White, Hispanic, Asian. By age 21, 54.1% (56.4% male, 51.9% female had initiated marijuana use – mean onset age 16.5 years.

2016 Martz et al found that marijuana use dampens brain response to reward over time. Measurable changes were found in the brain reward system with marijuana use even when other factors like alcohol and tobacco use were taken into account. 108 people in their early 20s, taking part in a larger study on substance abuse had brain scans at 3 points over 4 years (75% men, almost all white). In the moment of anticipating a reward (e.g. may win money) the nucleus accumbens (part of the reward system) pumps out dopamine (pleasure neurotransmitter), the greater the anticipation the more dopamine is produced. However the more marijuana used, the smaller the response over time. This suggests that long-term marijuana use dampens the emotional response of a person – anhedonia. These brain changes may increase the risk of continued drug use and addiction.

2016 Andrade produced a superb paper on the Use of cannabis and cannabinoids for medical purposes. He found that, relative to placebos, cannabinoids are associated with only modest benefits for chemotherapy-related nausea and vomiting, small and inconsistent benefits for pain and spasticity, and inconclusive benefits for other indications. In randomised controlled trials, cannabinoids increase the risk of total adverse events, serious adverse events and dropout due to adverse events. Cannabinoids also increase the risk of a large number of specific adverse effects.

2016 Scripps Institute research (Center for Psychological Studies) found striking discrepancies in how marijuana users perceived themselves versus how others perceived them. Cannabis users believed that the drug improved their self-awareness and thus enhanced their relationships with loved ones. In contrast, the perceptions of their family members revealed gross perceptual distortions, specifically in regards to interpersonal competence and emotional availability. Genuine intimacy, particularly between husband and wife or parent and child requires time, shared interests, and deep emotional connection – exactly the opposite of the vacant, isolated and depersonalised effect associated with cannabis. Research shows that users lack awareness of their loved one’s feelings, struggles, dreams, hopes and disappointments. Regular use of cannabis in young adults is indicative of multiple failed relationships. Emotional maturity appears to stop when cannabis use begins – measureable deficits in interpersonal skills, including empathy, acceptance, warmth and genuineness.

2016 Compton et al investigated marijuana use and disorders in adults in the USA 2002 – 2014.
Data from US civilians aged 18 years or older who participated in annual, cross-sectional US National Surveys on Drug Use and Health from 2002 to 2014 was analysed. The sample in each US state was designed to be approximately equally distributed between participants aged 12–17 years, 18–25 years, and 26 years or older. For each survey year, we estimated prevalence of marijuana use and use disorders, initiation of marijuana use, daily or near daily use, perception of great or no risk of harm from smoking marijuana, perception of state legalisation of medical marijuana use, and mean number of days of

marijuana use in the previous year. 596 500 adults participated in the 2002–14 surveys. Marijuana use increased from 10·4% to 13·3% in adults in the USA from 2002 to 2014, and the prevalence of perceiving great risk of harm from smoking marijuana once or twice a week decreased from 50· 4% to 33· 3%. Changes in marijuana use and risk perception generally began in 2006‑07. After adjusting for all covariates, changes in risk perceptions were associated with changes in prevalence of marijuana use, as seen in the lower prevalence of marijuana use each year during 2006‑14 than in 2002 when perceiving risk of harm from smoking marijuana was included in models. However, marijuana use disorders in adults remained stable at about 1· 5% between 2002 and 2014. Prevalence and frequency of marijuana use increased in adults in the USA starting in approximately 2007 and showing significantly higher results in multivariable models during 2011–14 (compared with 2002).

2016 Wang et al investigated unintentional paediatric exposures to marijuana in Colorado from 2009 to 2015. Colorado's Children's Hospital and Colorado's RPC (Regional Poison Centre) admissions were examined for 0 to 9 year olds between 2009 and 2015 for single-substance marijuana exposures. Of the 163 cases at the RPC, median age of exposure was 2 years and 85 (52%) were girls. Of the 81 Hospital admissions, median age was 2.4 years, 25 (40%) were girls. The mean rate of marijuana-related visits to the Hospital increased from 1.2/100,000 of the population 2 years prior to legalisation to 2.3%/100,000 2 years afterwards. Median length of stay was 11 hours and 26 hours for admitted patients, 48% were due to infused edibles. Annual RPC cases increased more than 5-fold from 2009 t0 2015. Colorado had an average increase of 34% in the RPC per year compared with the rest of the USA which had an increase of only 19%. Edible products were responsible for 52%, 9% were not in a child-proof container, poor supervision or product storage amounted to 34%. Almost half of the patients seen in the Hospital in the two years after legalisation were due to recreational cannabis, so legalisation, it is suggested, did affect the incidence of exposures.

2016 Itami et al gained scientific proof of the adverse effects of cannabis. 'Important mechanisms involved in the formation of neural circuits in the brain have now been revealed by a research team. This group also discovered that delta-9-tetrahydrocannabinol (THC), a psychoactive substance also found in cannabis, causes disruption of neural circuits within the cortex. These results explain why cannabis may be harmful and have potential to find application in the functional recovery of brain injury and in cases of dementia'.

2016 Sophocleous et al investigated cannabis use and bone density. Cross-sectional study of individuals recruited from primary care in the UK between 2011 and 2013. Cases were regular smokers of cannabis divided into moderate (n = 56) and heavy user (n = 144) subgroups depending on whether they reported fewer or more than 5000 cannabis smoking episodes during their lifetime. Controls comprised 114 cigarette smokers. They concluded that, 'Heavy cannabis use is associated with low bone mineral density, low BMI, high bone turnover, and an increased risk of fracture. Heavy cannabis use negatively impacts on bone health both directly and indirectly through an effect on BMI'.

2016 Conroy et al looked at sleep patterns and marijuana use. 98 subjects were split into 3 groups – daily users (49), once/month , up to 5 days/week (29) and a control group (20), of non-users. Most were in their early twenties, 45 were male and 53 female. While 20% of the non-smokers met the criteria for clinical insomnia, for daily users it was 39%, which was worse than occasional users. The researchers also cited a previous study showing that found an association between higher rates of use and anxiety that may be a factor in disrupted sleep. Women were worse affected than men.

2016 Wilson et al looked at the results of exposure to marijuana smoke in children. They tested for metabolites of marijuana in their urine. Forty-three healthy babies aged 1 month to two years, hospitalise for bronchiolitis in a Colorado hospital between 2013 and 2105. 16% were found to have COOH-THC in their urine. Of those parents who reported marijuana use or exposure in the home, 75% had detectable levels of COOH-THC in their urine. Higher concentrations were found in non-white as compared to white children.

2016 Schwitzer et al investigated the association between regular cannabis use and ganglion cell dysfunction. Their objective was to demonstrate whether the regular use of cannabis could alter the function of retinal ganglion cells in humans. 28 subjects were regular cannabis smokers and 24 non-users were controls. All were in their twenties. A small but significant delay was found in the time taken for the signals to be processed by the retina of the marijuana users by comparison with the control group.

2016 Medical letter on Drugs and Therapeutics. An account is given of the efficacy of marijuana extracts Nabilone (THC), Dronabinol (THC), Epidiolex (CBD) and Sativex (THC and CBD).

2016 Amen et al looked at low hippocampal blood flow and higher alzheimer's vulnerability in marijuana users. Persons with a diagnosis of cannabis use disorder by criteria (n=982) were compared to controls (n=92) with perfusion neuroimaging with SPECT at rest and at a concentration task. Marijuana users showed lower cerebral perfusion on average. Discriminant analysis distinguished marijuana users from controls with correct classification of 96%. With concentration SPECT regions, there was correct classification of 95%. The mRMR analysis showed right hippocampal hypoperfusion on concentration SPECT imaging was the most predictive in separating marijuana subjects from controls. They concluded that multiple brain regions show low perfusion on SPECT in marijuana users. The most predictive region distinguishing marijuana users from healthy controls, the hippocampus, is a key target of Alzheimer's disease pathology. This study raises the possibility of deleterious brain effects of marijuana use.

2016 Kosterman et al investigated parents' attitudes about marijuana use. Washington state in 2014 legalised marijuana for adults. Data from 395 participants recruited in a 30-year longitudinal study at age 10 in 1985 were analysed. Now parents they still live in the Washington area in 2014, they were asked to assess their perceptions of adolescent marijuana use.

'82% agreed that regular marijuana use is harmful to teens.
89% of respondents disapproved of marijuana use where children can see it.
93% disapproved of parental use while caring for children.
19% said they would allow high-school age children to decide whether or not to use marijuana , compared to 6%, answering the same question in 1991'.

2016 Kim et Monte looked at cananbis legalisation and its effect on emergency care. Not surprisingly, increased marijuana use after legalization has been accompanied by an increase in the number of ED visits and hospitalizations related to acute marijuana intoxication. Retrospective data from the Colorado Hospital Association, a consortium of more than 100 hospitals in the state, has shown that the prevalence of hospitalizations for marijuana exposure in patients aged 9 years and older doubled after the legalization of medical marijuana (15 per 100,000 hospitalizations in 2001 to 2009 versus 28 per 100,000 hospitalizations from 2010 to 2013; and that ED visits nearly doubled after the legalization of recreational marijuana (22 per 100,00 ED visits in 2010 to 2013 versus 38 per 100,000 ED visits from January to June of 2014.although these findings may be limited because of stigma surrounding disclosure of marijuana use in the prelegalization era. However, this same trend is reflected in the number of civilian calls to the Colorado poison control center. In the years after both medical and recreational marijuana legalization, the call volume for marijuana exposure doubled compared with that during the year before legalization (medical marijuana legalization: 44 calls in 2010 versus 95 calls in 2011, recreational marijuana legalization: 127 calls in 2013 versus 221 calls in 2014'.

2016 ElSohly et al looked at potency changes in cannabis over two decades. Marijuana is the most widely used illicit drug in the United States and all over the world. Reports indicate that the potency of cannabis preparation has been increasing. This report examines the concentration of cannabinoids in illicit cannabis products seized by DEA (drug and enforcement administration) over the last two decades, with particular emphasis on Δ9-THC and cannabidiol (CBD). Samples in this report are received over time from DEA confiscated materials and processed for analysis using a validated 'gas chromatograph with flame ionization detector (GC/FID)' method.A total of 38,681samples of cannabis preparations were received and analyzed between January 1, 1995 and December 31, 2014. The data showed that, while the number of marijuana samples seized over the last four years has declined, the number of sinsemilla samples has increased. Overall, the potency of illicit cannabis plant material has consistently risen over time since 1995 from approximately 4% in 1995 to approximately 12% in 2014. On the other hand, the CBD content has fallen on average from approximately 0.28% in 2001 to <0.15% in 2014, resulting in a change in the ratio of THC to CBD from 14 times in 1995 to approximately 80 times in 2014. It is concluded that there is a shift in the production of illicit cannabis plant material from regular marijuana to sinsemilla. This increase in potency poses higher risk of cannabis use, particularly among adolescents.

2016 Benedict et al investigated fungal infections in a commercially insured population of the US
2016 Case reports have identified invasive fungal diseasesin persons who use cannabis and fungal contamination of cannabis has been described. In a large health insurance claims data base, persons who used cannabis were 3.5 (95% CI 2.6- 4.8) times more likely than persons who did not use cannabisto have a fungal infection in 2012 Cannabis can contain fungal pathogens that cause serious and often fatal infections in persons with immunocompromising conditions, such as cancer, transplant, or infection with HIV (*1*). In

these patients, some reasons for using cannabis include pain and nausea relief and appetite stimulation. The frequency of fungal infections associated with cannabis is unknown but is a growing concern as more states legalize its medicinal and recreational use. We used health insurance claims data from 2016 to evaluate the prevalence of fungal infection In this large commercially insured population in the United States, cannabis use was associated with a higher prevalence of certain fungal infections. Although these infections were uncommon, they can result in substantial illness and even death, particularly in immunocompromised persons.diagnosis codes among persons who use cannabis and persons who do not use cannabis and to compare demographic and clinical features between these 2 groups. Conclusion: In this large commercially insured population in the United States, cannabis use was associated with a higher prevalence of certain fungal infections. Although these infections were uncommon, they can result in substantial illness and even death, particularly in immunocompromised persons.

2017 Thompson et al investigated medical marijuana for contaminants, moulds and bacteria. 20samples were purchased from North Carolina dispensaries and examined for the presence of micro-organisms. A wealth of diverse bacteria and fungi were discovered known to cause serious infections, especially in immuno-compromised patients, Aspergillus, Cryptococcus, Mucor, E. Coli, etc. Patients undergoing transplants or cancer therapies, uncontrolled diabetes, AIDS, or any condition involving a weakened or suppressed immune system are especially vulnerable. Dr Joseph Custano, a cancer specialist and professor in Hematology and Oncology at UC Davis said, 'Infections with the pathogens we found in medical marijuana could lead to serious illness and even death. Inhaling marijuana in any form provides a direct portal of entry deep into the lungs where infection can easily take hold'.

2017 Perucca looked at cannabinoids in the treatment of ecstasy, The interest in cannabis-based products for the treatment of refractory epilepsy has skyrocketed in recent years. Marijuana and other cannabis products with high content in Δ(9) - tetrahydrocannabinol (THC), utilized primarily for recreational purposes, are generally unsuitable for this indication, primarily because THC is associated with many undesired effects. Compared with THC, cannabidiol (CBD) shows a better defined anticonvulsant profile in animal models and is largely devoid of adverse psychoactive effects and abuse liability. Over the years, this has led to an increasing use of CBD-enriched extracts in seizure disorders, particularly in children. Although improvement in seizure control and other benefits on sleep and behavior have been often reported, interpretation of the data is made difficult by the uncontrolled nature of these observations. Evidence concerning the potential anti-seizure efficacy of cannabinoids reached a turning point in the last 12 months, with the completion of three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD product in patients with Dravet syndrome and Lennox-Gastaut syndrome. In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic, and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome. For the first time, there is now class 1 evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes. Based on currently available information, however, it is unclear whether the improved seizure control described in these trials was related to a direct action of CBD, or was mediated by drug interactions with concomitant medications, particularly a marked increased in plasma levels of N-desmethylclobazam, the active metabolite of clobazam. Clarification of the relative contribution of CBD to improved seizure outcome requires re-assessment of trial data for the subgroup of patients not comedicated with clobazam, or the conduction of further studies controlling for the confounding effect of this interaction.

2017Laporte et al looked at a brief intervention to reduce consumption in young cannabis users (15-25). In France, 77 general practitioners took part and 261 users were interviewed. After 1 year, there was no significant difference between the intervention and control groups in the median number of joints smoked per month among all users, but there was a difference in favor of the intervention among non-daily users . After 6 months, the intervention was associated with a more favorable change from baseline in the number of joints smoked (−33.3% vs 0%) and, among users younger than age of 18, smoking of fewer joints per month (12.5 vs 20).

2017 Milicic et al investigated the associations between E-cigarettes and binge drinking, marijuana use and energy drinks mixed with alcohol. Data from 39837 Canadian grade 9 to 12 students was used. 'Overall, 9.75% of respondents were current e-cigarette users. Current cigarette smokers (odds ratio [OR] = 3.009), current marijuana users (OR = 5.549), and noncurrent marijuana users (OR = 3.653) were more likely to report using e-cigarettes than non-cigarette smokers and non-marijuana users. Gender differences among males and females showed higher risk of e-cigarette use among female current marijuana users (OR = 7.029) relative to males (OR = 4.931) and female current smokers (OR = 3.284) compared to males (OR = 2.862). Compared to nonbinge drinkers, weekly (OR = 3.253), monthly (OR = 3.113), and

occasional (OR = 2.333) binge drinkers were more likely to use e-cigarettes. Similarly, students who consume energy drinks mixed with alcohol (OR = 1.650) were more likely to use e-cigarettes compared to students who do not consume them'. 'Youth who binge drink or use marijuana have a greater increased risk for using e-cigarettes compared to cigarette smokers. These data suggest that efforts to prevent e-cigarette use should not only be discussed in the domain of tobacco control'.

2017 Kristman-Valente et al looked at the relationship between marijuana and conventional cigarette smoking behaviour from early adolescence to adulthood. 'Marijuana use and conventional cigarette smoking were associated within time in decreasing magnitude and increased cigarette smoking predicted increased marijuana use during adolescence. A reciprocal relationship was found in the transition from young adulthood to adulthood, such that increased conventional cigarette smoking at age 24 years uniquely predicted increased marijuana use at age 27 years, and increased marijuana use at age 24 years uniquely predicted more frequent conventional cigarette smoking at age 27 years, even after accounting for other factors'.

2017 Blundell et al Warned of the 'dark cloud of recreational drugs and vaping'. 'Electronic cigarettes are increasing in popularity with 19% of UK smokers reporting to have used them. The ability to regulate the evaporation temperature in newer electronic nicotine delivery systems (ENDS) facilitates the potential for use of these devices to 'vape' cannabis. Vaping cannabis does have the potential to reduce tobacco use and combustible cannabis/tobacco-related disease, but with over one-third of UK adults reporting lifetime use of recreational drugs and increasing e-cigarette uptake in adolescent groups the misuse of these devices poses a serious potential public health risk'.

2017 Mills et al looked at child maltreatment and cannabis use in young adulthood. A birth cohort of 7223 mother and child pairs were studied. Of these, 3778of the young people participated at age 21. After confounder adjustment, substantiated child maltreatment was associated with any life-time cannabis use (OR) = 1.60, cannabis use prior to age 17 (OR = 2.47), daily cannabis use (OR = 2.68) and DSM-IV cannabis abuse/dependence (OR = 1.72). Externalizing behaviour and tobacco and alcohol use at age 14 were associated significantly with almost all cannabis outcomes, with internalizing behaviour associated inverse).

2017 Miech et al found that college attendance was a risk factor for cannabis use. 'Data come from the Monitoring the Future study, which has followed longitudinal panels drawn from annual nationally representative, baseline samples of 12th-grade students starting with the class of 1976. We studied panel members aged 19 to 22 years who had never used marijuana by 12th grade between 1977 and 2015. *Results.* College as a risk factor for marijuana initiation has increased significantly since 2013. The increased probability of past-year marijuana use for those enrolled versus not enrolled in college was 51% in 2015, 41% in 2014, and 31% in 2013; it averaged 17% to 22% from 1977 to 2012 among youths who had never used marijuana by 12th grade. Conclusin: College has grown as a risk factor for marijuana initiation since 2013'.

2017 Campbell et al looked at socioeconomic status and adverse birth outcomes. A study in London Ontario found that women who used marijuana during pregnancy were almost 3 times as likely to have an infant with low birth weight. Amphetamine use, chronic hypertension and smoking were also identified as other top risk factors for low birth weights. Low birth weight can lead to respiratory problems and asthma, poor cognitive development and type 2 diabetes, hypertension and cardiovascular disease later in life. Socioeconomic factors had little effect on birth outcomes. A birth weight of less than 2500grams was classed as low weight. The rate for this study was 6.4%.

2017 Wang et al found that emergency visits related to marijuana use at Colorado hospital had quadrupled from 2005 to 2014. Care records for 13 t0 21 year olds showed that visits rose from 146 t0 639. Adolescents with symptoms of mental illness accounted for 66% of the 3,443 marijuana-related visits. Psychiatry consultations increased from 65 to 442.

2017 Association for Research in Vision and Opthalmology (ARVO) Paper found that prenatal exposure to marijuana may have lasting effects on vision. 'Pregnant mice were exposed daily throughout the entire pregnancy to either marijuana smoke (in doses that mimic human exposure) or to filtered air. After birth, the newborn mice were evaluated at three, six and 12 months of age. The retinas of mice whose mothers had been exposed pre-natally to marijuana were significantly thinner. The findings further suggested that the retinas thickness did not normalize as the mice aged. The retina is part of the central nervous system

and little is known about the effects of maternal cannabis use on retinal development on the offspring and its potential postnatal consequences'

2017 Gilbert et al looked at intravenous administration of cannabis and lethal anaphylaxis. 'A 33-year-old woman is reported who collapsed and died shortly after injecting herself with a cannabis solution prepared by pouring boiling water onto plant material. There were no significant findings at autopsy, except for a single recent venepuncture wound in the left cubital fossa. Toxicological examination of the blood revealed low levels of methylamphetamine and amphetamine with tetrahydrocannabinol (Δ9-THC) and 11-nor-9-carboxy-Δ9-THC, and no opiates. The syringe used by the decedent contained Δ9-THC. Serum tryptase levels were markedly elevated. This finding coupled with the sudden collapse after injecting an aqueous extract of cannabis indicated a likely anaphylactic or anaphylactoid reaction to the extract. Cannabis allergy may occur following handling, inhalation, swallowing or injecting Cannabis sativa plants or their products. The possibility of an allergic reaction should therefore be considered at autopsy in deaths where there has been recent contact with cannabis'.

2017 Polat et al looked at corneal changes in long-term cannabinoid users. 'The study enrolled 28 eyes of 28 patients diagnosed with cannabinoid use disorder. The cannabinoid group was selected among patients who had been using the substance for 3 days or more per week over the past 1 year. 32 eyes of 32 age- and sex-matched healthy individuals enrolled as control group in the study. Corneal endothelial cell density (CD), coefficient of variation (CV) and hexagonal cell ratio (HEX) values were analyzed by specular microscopy. RESULTS: The mean CD was 2900±211 cells/mm2 in the cannabinoid group and 3097±214 cells/mm2 in the control group. There was a significant decrease in cannabinoid group. No significant difference was present between the cannabinoid and the control groups in terms of mean CV value. There was not a significant difference between the cannabinoid and the control groups in terms of mean HEX value. A significant decrease in CD was found in cannabinoid users compared the control group'.

2017 Chan et al looked at attitudes and marijuana beliefs among Colorado medical students. 'Medical students (n = 624) at the University of Colorado School of Medicine between January and February 2014 were invited to participate. We received 236 responses (37%). Students indicated support for marijuana legalization (64%), and few believed that physicians should be penalized for recommending marijuana to patients (6%). Nearly all (97%) believed that further marijuana research should be conducted, and believed marijuana could play a role in the treatment of various medical conditions. Seventy-seven percent reported that they believed marijuana use had the potential for psychological harm, and 68% indicated concern for potential physical harm. Only a minority of students would recommend marijuana to a patient under current law (29%), or if it were legally available (45%). Acceptability of marijuana for treatment of approved conditions was not correlated with age or gender, but was positively correlated with living in Colorado prior to medical school and with prior marijuana use. They concluded that medical students support marijuana legal reform, medicinal uses of marijuana, and increased research, but have concerns regarding risks of marijuana use, and appear hesitant to recommend marijuana to patients'.

2017 Bull et al looked at the awareness, perception of risk and behaviours related to retail marijuana among a sample of Colorado youth. 'Youth marijuana use is a growing concern with increasingly permissive views towards marijuana use. Little is known about attitudes and beliefs toward marijuana use among youth in the context of legalization. This study describes youth attitudes and beliefs about health risks associated with marijuana use, social norms of peer use, conversations with parents about marijuana use, and knowledge of recreational marijuana laws, using a venue-day-time sampling approach with diverse Colorado youth (n = 241) post-legalization. We considered demographic (gender, racial/ethnic and geographic) differences in knowledge of laws and perceptions of risk. While many youth are knowledgeable about retail marijuana laws in Colorado, males were 2.12 times more likely to be familiar with laws compared to females. While 40 % of the sample perceived a moderate to high risk from weekly marijuana consumption and 57 % from daily consumption, fewer males perceived these risks. Over ¾ of the sample indicate they discuss marijuana with parents, but many fewer indicate discussing consequences and health effects of use with parents. Results suggest opportunities for parents and clinicians to influence youth attitudes and behaviors towards marijuana use. It may be worthwhile to target educational campaigns to different demographic groups, and to offer training and capacity building for parents to discuss marijuana with their teenaged children'.

2017 Claudet et al conducted a 10 year review of cannabis exposure in children under 3-years of age. Abstract: Pediatricians working in an emergency environment are confronted with children admitted to emergency departments for intoxication on a daily basis. We carried out a retrospective cohort study of children admitted to a pediatric emergency department due to unintentional cannabis exposure over a 10-year period from 2004 to 2014. Twenty-nine children under the age of 3 were admitted with a positive cannabis urine test. Eighty-seven percent of intoxications occurred at the family home. Resin was the main

form of ingested cannabis (69%). The mean age was 16.5 ± 5.2 months, and mean weight was 11.1 ± 2.1 Kg. Sixty percent of admissions occurred between 2012 and 2014. More severe presentations, based on Poisoning Severity Score, occurred over the past 2 years. Four children experienced seizures before admission. Ten children (34%) had a decreased level of consciousness (GCS <12) and were admitted to a pediatric intensive care unit for 12-24 h. All of them had ingested hashish (resin). The majority (70%) of children suffering from neurological impairment were admitted in the last year, of whom three required assisted ventilation. There were no cases with major outcomes and no deaths. Parents were not assessed regarding their cannabis consumption.

CONCLUSION: This study supports the impression that accidental child poisonings with cannabis have been more serious than previously thought for 2 years. This observation may be explained by (1) the increased THC concentration in cannabis and (2) the widespread use in young adults, even after they become parents. Introducing an addiction team inside the PED could help to improve the care links with these parents. What is Known: • Cases of unintentional cannabis intoxication in children have been increasing for many years due to an increase of potency. What is New: • We highlight an increase in more severe presentations in children under the age of 3 occurring over the past 2 years, which will indicate the importance of assessing cannabis abuse in parents by a specialized addiction team.

2017 Popova et al looked at perceived harms and benefits of tobacco, marijuana and electronic vaporisers among young adults in Colorado**. Abstract:** Participants were thirty-two young adults (18-26 years old) who used tobacco/marijuana/vaporizers. Semi-structured interviews addressed perceived harms and benefits of various tobacco and marijuana products and personal experiences with these products. FINDINGS: Young adults evaluated harms and benefits using five dimensions: (1) Combustion - smoking was considered more harmful than non-combustible products (e.g., e-cigarettes, vaporizers, and edibles); (2) Potency - edibles and marijuana concentrates were perceived as more harmful than smoking marijuana flower because of potential to receive too large a dose of THC (tetrahydrocannabinol); (3) Chemicals - products containing chemical additives were seen as more harmful than "pure" or "natural" plant products; (4) Addiction - participants recognized physiological addiction to nicotine, but primarily talked about psychological or lifestyle dependence on marijuana; (5) Source of knowledge - personal experiences, warning labels, campaigns, the media, and opinions of product retailers and medical practitioners affected perceptions of harms and benefits. Conclusion: Among young adults in Colorado, USA, perceived harms and benefits of tobacco and marijuana include multiple dimensions. Health educational campaigns could benefit from addressing these dimensions, such as the potency of nicotine and cannabis concentrates and harmful chemicals present in the organic material of tobacco and marijuana. Descriptors such as "natural" and "pure" in the promotion or packaging of tobacco and marijuana products might be misleading.

2017 Montanari et al reported on significantly growing numbers of people entering drug treatment in Europe for cannabis-related problems. The data from 22 countries from 2003 to 2014 were used. Overall increase of cannabis treatment entries is continuous although country-related differences are observed. Possible explanations include: increase in prevalenceand cannabis-related problems, changes in risk perception, increases in cannabis potency, changes in referral practice and increased availability and accessibility of treatment services.

2017 Shariff et al found that cannabis, used often was a risk for gum disease. Data came from 1938 US adults who participated in the Center for Disease Control's 2011-2012 National Health and Nutrition Examination Survey, 27% admitted using cannabis one or more times for at least 12 months. Healthy gums fit a tooth snugly (no more than 1- 3mm space, known as pocket depth, between tooth and surrounding gum tissue. Wider pockets usually indicate the presence of periodontitis. Frequent cannabis uses had more sites with pocket depths indicative of moderate to severe periodontal disease compared to less frequent users. After controlling for confounding factors, frequent recreational cannabis users are twice as likely as non-frequent users to have periodontal disease.

2017 Findings (Drug and Alcohol) – Young People's statistics from the Nat. Drug Treatment Monitoring System (NDTMS) 1s April 2015 to 31st March 2016. 'The diminishing youth treatment caseload in England is increasingly dominated by under-18s primarily being treated for cannabis use problems as the numbers of primary problem drinkers falls away to just 15% of the caseload. 87% of young people in specialist services say they have a problem with this drug.

2017 Windle et al studied social influences on college student use of tobacco products, alcohol and marijuana. '3,418 college students from seven universities in the state of Georgia participated in this study. For each tobacco product or substance, the highest associations were for friends' use. Similar to findings with adolescents, the use of alternative tobacco products, alcohol, and marijuana by parents, siblings, and

friends is associated with higher levels of use among college students, and friends' use was the most potent correlate for this phase of the lifespan'.

2017 Kendler et al looked at drug-associated mortality across the lifespan. 'We examined all individuals born in Sweden 1955-1980 (n = 2,696,253), 75,061 of whom developed DA (Drug Abuse). The mortality hazard ratio (mHR) for DA was 11.36, substantially higher in non-medical (18.15), than medical causes (8.05), and stronger in women (12.13) than in men (11.14). Comorbid smoking and alcohol use disorder explained only a small proportion of the excess DA-associated mortality. Co-relative analyses demonstrated substantial familial confounding in the DA-mortality association with the strongest direct effects seen in middle and late-middle ages. The mHR was highest for opiate abusers (24.57), followed by sedatives (14.19), cocaine/stimulants (12.0), and cannabis (10.93)'.

2017 Friese et al explored the use of marijuana edibles by adolescents in California. Abstract: 'We analyzed California Healthy Kids Survey data collected in one Northern California school district with a racially and ethnically diverse student population. Survey respondents were youth in grades 9-12. Overall, 33% of respondents reported having used marijuana in their lifetime, and 50% of lifetime marijuana users reported using marijuana in the past 30 days. Seventy-two percent of lifetime marijuana users and 82% of past month marijuana users reported having used edibles in their lifetime. Comparing marijuana users who have never used edibles to those users who have, we found that edible users reported using marijuana more frequently in their lifetime. Edible users were also more likely to have used marijuana in the past 30 days, more frequently in the past 30 days, more likely on school property and more frequently on school property. Edible users and non-users differed in their perceptions of risk; edible users were less likely to agree that edible use is very risky. Edible users also reported a younger age of first marijuana use and more attempts to stop using marijuana than non-edible users. Multi-level regression analyses indicate that prevalence of edible use among marijuana users was related to perceived risk of edible use. Perceived risk of edible use among marijuana users was higher among marijuana users who do not use edibles, females, and those youth who perceive school rules to be clear. The findings indicate that prevalence of edible use is high among marijuana users, especially frequent users.

2017 Gourdet et al examined how 4 US States regular recreational marijuana edibles. 'State laws governing recreational marijuana edibles have evolved since the first recreational edible products were available for sale. Alaska, Colorado, Oregon, and Washington now require edible product labels to disclose a variety of product information, including risk factors associated with consumption. However, there still remain concerns about the regulatory gaps that exist in each of these states, inherent difficulties in enforcing laws around the labelling, packaging, and manufacturing of edibles, and the outstanding question of whether these edible laws are actually informing consumers and keeping the public safe. Alaska, Colorado, Oregon, and Washington vary greatly in how they regulate labelling and packaging. Colorado, Oregon and Washington require a Universal Symbol to be affixed to edibles, but only Oregon and Washington require that the use of pesticides be disclosed on the label. Only Colorado and Oregon require that the packaging for edibles bear a Nutrition Facts Panel on the label. Δ9-Tetrahydracannabinol (THC) in a single serving or single edible product as Alaska and Oregon. All four states prohibit the manufacture or packaging of edibles that appeal to youth'.

2017 Paschall et al looked at medical marijuana use and legalisation in Oregon. Abstract: 'While the legalization of marijuana for medical and recreational use has raised concerns about potential influences on marijuana use and beliefs among youth, few empirical studies have addressed this issue. We examined the association between medical marijuana patients and licensed growers per 1000 population in 32 Oregon counties from 2006 to 2015, and marijuana use among youth over the same period. We obtained data on registered medical marijuana patients and licensed growers from the Oregon Medical Marijuana Program and we obtained data on youth marijuana use, perceived parental disapproval, and demographic characteristics from the Oregon Healthy Teens Survey. Across 32 Oregon counties, the mean rate of marijuana patients per 1000 population increased from 2.9 in 2006 to 18.3 in 2015, whereas the grower rate increased from 3.8 to 11.9. Results of multi-level analyses indicated significant positive associations between rates of marijuana patients and growers per 1000 population and the prevalence of past 30-day marijuana use, controlling for youth demographic characteristics. The marijuana patient and grower rates were also inversely associated with parental disapproval of marijuana use, which decreased from 2006 to 2015 and acted as a mediator. These findings suggest that a greater number of registered marijuana patients and growers per 1000 population in Oregon counties was associated with a higher prevalence of marijuana use among youth from 2006 to 2015, and that this relationship was partially attributable to perceived norms favorable towards marijuana use'.

2017 Corroon et al investigated the use of cannabis as a substitute for prescription drugs. 'A total of 2,774 individuals in Washington State were a self-selected convenience sample who reported having used

cannabis at least once in the previous 90 days. Subjects were surveyed via an online anonymous questionnaire on cannabis substitution effects. A total of 1,248 (46%) respondents reported using cannabis as a substitute for prescription drugs. The most common classes of drugs substituted were narcotics/opioids (35.8%), anxiolytics/benzodiazepines (13.6%) and antidepressants (12.7%). A total of 2,473 substitutions were reported or approximately two drug substitutions per affirmative respondent. The odds of reporting substituting were 4.59, greater among medical cannabis users compared with non-medical users and 1.66 greater among those reporting use for managing the comorbidities of pain, anxiety and depression. A slightly higher percentage of those who reported substituting resided in states where medical cannabis was legal at the time of the survey (47% vs. 45%,), but this difference was not statistically significant'.

2017 Henry looked at early onset of drug use among fathers with alcohol and cannabis use disorders. 'The children of fathers who met the criteria for a lifetime cannabis use disorder were more likely to initiate use of alcohol (odds ratio = 6.71) and cannabis (odds ratio = 8.13) by age 15, when background covariates and presence of a lifetime alcohol use disorder were controlled for. No unique effect of fathers' alcohol use disorder on children's onset of alcohol and cannabis use was observed. Fathers' lifetime cannabis use disorder had a unique and robust association with children's uptake of alcohol and cannabis by age 15.

2017 Borodovsky et al found that legal cannabis laws impact teen use. Data from Facebook (data from Facebook (2630 cannabis-using youths aged 14 – 18) was used to discover that adolescents living in medical marijuana states with a plethora of dispensaries are more likely to have tried new methods of cannabis use such as vaping and edibles. This happens at a younger age than those living in states with fewer dispensaries.

2017 Al-Shammari et al looked at the Effects of the 2009 Medical Cannabinoid Legalization Policy on Hospital Use for Cannabinoid Dependency and Persistent Vomiting. 'We observed an increasing trend of CDU or an aggregate of CDU and persistent vomiting during the pre-legalization period. The legalization of marijuana significantly increased the incidence rate during the legalization period (by 17.9%) and the yearly average increase in rate by 6% after policy implementation, compared to the pre-legalization period. The increase in rate of persistent vomiting after policy implementation increased significantly (by about 8%), although there were no significant trends in increase prior to or during marijuana legalization in 2009'.

2017 Patrick et al looked at High-intensity and simultaneous alcohol and marijuana use among high school seniors in the U.S. 'Data come from nationally representative samples of U.S. 12th graders who participated in the Monitoring the Future study from 2005 to 2014 (N = 24,203 respondents; 48.4% boys, 51.6% girls). Results: SAM use during the past year was reported by 20% of 12th graders overall. SAM use prevalence was strongly and positively associated with alcohol and marijuana use intensity even after controlling for covariates. High school seniors at highest risk for engaging in SAM use were those who reported 10+ drinks and those smoking at least 1 joint/day. Approximately 60% of those who had 10-14 or 15+ drinks in a row during the past two weeks and 76-80% of those who had 1 or 2+ joints per day on average during the past 30 days reported SAM use.Results suggest that high school seniors who consume high quantities of alcohol and marijuana are very likely to consume these substances so that their effects overlap'.

2017 O'Brien et al looked at post-high school changes in tobacco and cannabis use in The UnitedStates. Living in a dorm/fraternity/sorority was associated with an increased prevalence in cannabis use while attending a 4-year college was associated with a decreased prevalence in cigarette use.

2017 Tomassi et al studied the influence of childhood trauma on diagnosis and substance use in first-episode psychosis. They aimed **'**To test whether people with first-episode psychosis who had experienced childhood trauma, when compared with those who had not, showed a higher rate of affective psychosis and an increased lifetime rate of substance use. The sample comprised 345 participants with first-episode psychosis (58% male, mean age 29.8 years). Severe sexual abuse was significantly associated with a diagnosis of affective psychosis ($\chi 2 = 4.9$, $P = 0.04$) and with higher rates of lifetime use of cannabis (68% *v* 41%; $P = 0.02$) and heroin (20% *v* 5%; $P = 0.02$). Severe physical abuse was associated with increased lifetime use of heroin (15% *v* 5%; $P = 0.03$) and cocaine (32% *v* 17%; $P = 0.05$)'. They concluded that **'**Patients with first-episode psychosis exposed to childhood trauma appear to constitute a distinctive subgroup in terms of diagnosis and lifetime substance use'.

2017 Mason et al looked at the influence of close friends and substance abuse. 'Results implicate the importance of understanding problematic peer behavior within the context of close, adolescent friendships. Adolescents with close friends who were substance users, who made offers to use substances, and who engaged in risky behaviors were more likely to use tobacco and cannabis. Perceptions of young adolescents' close friends' behaviors influenced their substance use up to 2 years later. (PsycINFO Database Record'

2017 Casajuana et al investigated 'the standard joint unit'. '492 participants donated 315 valid joints. Donators were on average 29 years old, mostly men (77%), single (75%), with at least secondary studies (73%) and in active employment (63%). Marijuana joints (N=232) contained a median of 6.56mg of 9-THC (Interquartile range-IQR=10,22) and 0.02mg of CBD (IQR=0.02); hashish joints (N=83) a median of 7.94mg of 9-THC (IQR=10,61) and 3.24mg of CBD (IQR=3.21). Participants rolled 4 joints per gram of cannabis and paid 5€ per gram (median values). Consistent 9-THC-content in joints lead to a SJU of 7mg of 9-THC, the integer number closest to the median values shared by both cannabis types. Independently if marijuana or hashish, 1 SJU = 1 joint = 0.25 g of cannabis = 7 mg of 9-THC. For CBD, only hashish SJU contained relevant levels. Similarly to the Standard Drink Unit for alcohol, the SJU is useful for clinical, epidemiological and research purposes'.

2017 Ford et al produced an overview of cannabis, its adverse acute and chronic effects and their implications.

Abstract: 'In many communities, cannabis is perceived as a low-risk drug, leading to political lobbying to decriminalise its use. However, acute and chronic cannabis use has been shown to be harmful to several aspects of psychological and physical health, such as mood states, psychiatric outcomes, neurocognition, driving and general health. Furthermore, cannabis is highly addictive, and the adverse effects of withdrawal can lead to regular use. These in turn have adverse implications for public safety and health expenditure. Although the cannabinoid cannabidiol (CBD) has been shown to have positive health outcomes with its antioxidant, anticonvulsant, anti-inflammatory and neuroprotective properties, high-potency cannabis is particularly damaging due to its high tetrahydrocannabinol (THC), low CDB concentration. It is this high-potency substance that is readily available recreationally. While pharmaceutical initiatives continue to investigate the medical benefits of CDB, "medicinal cannabis" still contains damaging levels of THC. Altogether, we argue there is insufficient evidence to support the safety of cannabis and its subsequent legalisation for recreational use. Furthermore, its use for medicinal purposes should be done with care. We argue that the public conversation for the legalisation of cannabis must include scientific evidence for its adverse effects'.

2017 Lee et al Looked at the trajectories of cannabis use beginning in adolescence associated with symptoms of PTSD in the mid-thirties. 'Growth mixture modelling was conducted to identify the cannabis use trajectory groups using a community sample of 674 participants (53% African Americans, 47% Hispanics of Puerto Rican decent; 60% females) from the Harlem Longitudinal Development Study. Logistic regression analyses were performed to examine the association between earlier trajectories of cannabis use (ages 14 to 36) and later symptoms of PTSD (at age 36) for the full model including the entire sample (N = 674) as well as the reduced model including only participants who had experienced a traumatic event (n = 205). Five trajectory groups of cannabis use were obtained. The chronic use group (full model: adjusted odds ratio [AOR] = 4.68, reduced model: AOR = 4.27, the late quitting group (full model: AOR = 6.18, reduced model: AOR = 6.67, and the moderate use group (full model: AOR = 3.97, reduced model: AOR = 3.32) were all associated with an increased likelihood of having PTSD symptoms at age 36 compared with the no use group.The findings provide information that PTSD symptoms in the mid-30s can possibly be reduced by decreasing membership in the chronic cannabis use trajectory group, the late quitting trajectory group, and the moderate cannabis use trajectory group'.

2017 Choi et al investigated nonmedical versus medical marijuana use among 3 age groups of adults, 'Given that 29 U.S. states now have laws allowing medical marijuana use, this study examined mental and physical health correlates of medical versus non-medical marijuana use among three age groups of adults (18-29, 30-49, and 50+). Data came from the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions (N = 36,309 respondents aged 18+). Of all respondents, 9.74% (N = 3,784) reported past-year marijuana use. Of all past-year marijuana users, 11.03% (n = 445) reported medical use. Medical marijuana use rates were higher among the 50-64 age group (17.95%) than younger adults, and 32.88% of medical users, compared to 25.25% of non-medical users, had past-year marijuana use disorder. The odds of medical marijuana use were higher among those with marijuana use disorder (OR = 1.87) and personality disorder (OR = 1.42), with no age group differences. However, older adults with alcohol use disorder and sleep problems and middle-age adults with arthritis had diminished odds of having used medical marijuana relative to young adults. Given the high rates of marijuana use disorder among medical users, physicians should exercise caution in recommending marijuana for medical purposes, especially for younger adults. More research is needed on medical marijuana's safety and efficacy for patients at risk of marijuana use disorder. (Am J Addict 2017;XX:1-10).

2017 Hernandez et al looked at hyperemesis. 'Cannabinoid hyperemesis syndrome (CHS) is a paradoxical side effect of cannabis use. Patients with CHS often present multiple times to the emergency department

(ED) with cyclical nausea, vomiting, and abdominal pain, and are discharged with various misdiagnoses. CHS studies to date are limited to case series. The objective was to examine the epidemiology of CHS cases presenting to two major urban tertiary care centre EDs and one urgent care centre over a 2-year period. Using explicit variables, trained abstractors, and standardized abstraction forms, we abstracted data for all adults (ages 18 to 55 years) with a presenting complaint of vomiting and/or a discharge diagnosis of vomiting and/or cyclical vomiting, during a 2-year period. We identified 494 cases: mean age 31 (+/-11) years; 36% male; and 19.4% of charts specifically reported cannabis use. Among the regular cannabis users (>three times per week), 43% had repeat ED visits for similar complaints. Moreover, of these patients, 92% had bloodwork done in the ED, 92% received intravenous fluids, 89% received antiemetics, 27% received opiates, 19% underwent imaging, 8% were admitted to hospital, and 8% were referred to the gastroenterology service. This study suggests that CHS may be an overlooked diagnosis for nausea and vomiting, a factor that can possibly contribute to unnecessary investigations and treatment in the ED. Additionally, this indicates a lack of screening for CHS on ED history, especially in quantifying cannabis use and eliciting associated symptoms of CHS'.

2017 Nugent et al looked at cannabis and chronic pain. Cannabis is increasingly available for the treatment of chronic pain, yet its efficacy remains uncertain. DATA SOURCES: MEDLINE, Cochrane Database of Systematic Reviews, and several other sources from database inception to March 2017. From 27 chronic pain trials, there is low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations. Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain.

2017 Claudet et al looked at unintentional cannabis intoxication in toddlers. 'In France, cannabis consumption is illegal. The health impact of its increasing use and higher tetrahydrocannabinol (THC) concentrations is still poorly documented, particularly that of unintentional pediatric intoxications. We sought to evaluate the French national trend of admissions for unintentional cannabis intoxication in children over an 11-year period (2004-2014). A retrospective, national, multicenter, observational study of a pediatric cohort. All children aged <6 years admitted to a tertiary-level pediatric emergency department (PED) for proven cannabis intoxication (compatible symptoms and positive toxicological screening results) during the reference period were included. Twenty-four PEDs participated in our study; 235 children were included, and 71% of the patients were 18 months old or younger. Annual admissions increased by a factor of 13. Hashish resin was the main form ingested (72%). During the study period, the evolution was characterized by a national increase in intoxications, younger intoxicated children (1.28 ± 0.4 vs 1.7 ± 0.7 years), and more comas ($n = 38$) (odds ratio 3.5 [1.02-11.8]). Compared with other intoxications, other PED admissions, and the same age population, cannabis-related admissions were greater. There was a potential link between the increased incidence of comas and increased THC concentration in resin seized in France over the period. Children are collateral victims of changing trends in cannabis use and a prevailing THC concentration. Intoxicated children are more frequent, are younger, and have intoxications that are more severe. This raises a real issue of public health'.

2017 Brooks et al looked at the clinical implications of legalising marijuana to see if Physicians etc are prepared. 'We surveyed 114 Colorado-based providers who care for children, adolescents, pregnant and breastfeeding women using a Venue-Day-Time survey methodology throughout Colorado. The survey captured providers' (e.g., physicians, nurses, medical assistants) knowledge of state marijuana laws, risk perceptions, counselling practices, and continued training needs. Providers were knowledgeable about marijuana laws, cautious supporting legalization, and perceived moderate to high risks, particularly for certain groups. About 50% of providers working with adolescents and pregnant or breastfeeding women assessed marijuana use "every" or "most" visits; 23% of those working with children reported such behaviour. Conversations about specific risks varied between groups. Few providers felt completely knowledgeable about marijuana health risks and lacked confidence talking to patients about this issue. CONCLUSIONS:Providers frequently assess patients' marijuana use; however, they are uncomfortable and inconsistent talking to patients about specific marijuana health effects. Additional education is warranted, particularly as it relates to talking to patients about the danger of second hand smoke exposure, underage use, safe storage, and the over-consumption of edibles'.

2017 Barkin et al investigated cannabis-induced acute pancreatitis. 'Cannabis was first reported as a possible cause of acute pancreatitis (AP) in 2004. A search using PubMed/Medline, Embase, Scopus, and Cochrane was performed without language or year limitations to May 1, 2016. Search terms were "Cannabis" and "Acute Pancreatitis" with all permutations. The search yielded 239 results. Acute pancreatitis was defined by meeting 2 of 3 Revised Atlanta Classification criteria. Cannabis-induced AP was defined by preceding use of cannabis and exclusion of common causes of AP when reported. Sixteen papers met inclusion criteria dating from 2004 to 2016.There were 26 cases of cannabis-induced AP (23/26

men; 24/26 under the age of 35 y). Acute pancreatitis correlated with increased cannabis use in 18 patients. Recurrent AP related temporally to cannabis use was reported in 15 of 26. There are 13 reports of no further AP episodes after cannabis cessation. Cannabis is a possible risk factor for AP and recurrent AP, occurring primarily in young patients under the age of 35 years. Toxicology screens should be considered in all patients with idiopathic AP'.

2017 Richards et al looked at unintentional cannabis ingestion in children. PubMed, OpenGrey, and Google Scholar were systematically searched. Articles were selected, reviewed, and graded using Oxford Center for Evidence-Based Medicine guidelines. Of 3316 articles, 44 were included (3582 children age ≤12 years). We found no high quality (Oxford Center for Evidence-Based Medicine level I or II) studies and 10 level III studies documenting lethargy as the most common presenting sign and confirming increasing incidence of unintentional ingestion in states having decriminalized medical and recreational cannabis. We identified 16 level IV case series, and 28 level V case reports with 114 children, mean age 25.2 ± 18.7 months, range 8 months to 12 years, and 50 female children (44%). The most common ingestion (n = 43, 38%) was cannabis resin, followed by cookies and joints (both n = 15, 13%). Other exposures included passive smoke, medical cannabis, candies, beverages, and hemp oil. Lethargy was the most common presenting sign (n = 81, 71%) followed by ataxia (n = 16, 14%). Tachycardia, mydriasis, and hypotonia were also commonly observed. All cases were cared for in the emergency department or admitted, and mean length of stay was 27.1 ± 27.0 hours. Twenty (18%) were admitted to the pediatric intensive care unit, and 7 (6%) were intubated. Unintentional cannabis ingestion by children is a serious public health concern and is well-documented in numerous studies and case reports. Clinicians should consider cannabis toxicity in any child with sudden onset of lethargy or ataxia'.

2017 Waldinger et al reported a case of cannabis-induced spontaneous orgasm. 'A case is described of a 40 year old woman with persistent spontaneous orgasms after use of Cannabis and five hour hard pounding sexual activity. She presented with severe anxiety in particular to suffer from Restless Genital Syndrome (ReGS). However, she did not fulfill to any of the five criteria of ReGS. It was concluded that her spontaneous orgasms were the result of the use of Cannabis combined with long duration of previous sexual activity. This is not only important for physicians but also for highly exposed subjects like those active in the sex industry'.

2017 Evanoff et al found that physicians in training are not prepared to prescribe medical cannabis. 'While medical marijuana use is legal in more than half of U.S. states, evidence is limited about the preparation of physicians-in-training to prescribe medical marijuana. We asked whether current medical school and graduate medical educational training prepare physicians to prescribe medical marijuana. We conducted a national survey of U.S. medical school curriculum deans, a similar survey of residents and fellows at Washington University in St. Louis, and a query of the Association of American Medical Colleges (AAMC) Curriculum Inventory database for keywords associated with medical marijuana. Surveys were obtained from 101 curriculum deans, and 258 residents and fellows. 145 schools were included in the curriculum search. The majority of deans (66.7%) reported that their graduates were not at all prepared to prescribe medical marijuana, and 25.0% reported that their graduates were not at all prepared to answer questions about medical marijuana. The vast majority of residents and fellows (89.5%) felt not at all prepared to prescribe medical marijuana, while 35.3% felt not at all prepared to answer questions, and 84.9% reported receiving no education in medical school or residency on medical marijuana. Finally, only 9% of medical school curriculums document in the AAMC Curriculum Inventory database content on medical marijuana. Our study highlights a fundamental mismatch between the state-level legalization of medical marijuana and the lack of preparation of physicians-in-training to prescribe it. With even more states on the cusp of legalizing medical marijuana, physician training should adapt to encompass this new reality of medical practice.

2017 Giombi et al asked consumer's for their perceptions of edible marijuana products for recreational use – likes, dislikes and reasons. 'The goal of this research was to provide a better understanding of consumer perceptions of edible marijuana products, including why they prefer edibles relative to other forms of marijuana (e.g., smoking) and their concerns regarding the consumption of edibles. We conducted eight focus groups (four groups in Denver, Colorado, and four groups in Seattle, Washington) in February 2016 with 62 adult consumers of edibles. Most participants preferred edibles to smoking marijuana because there is no smell from smoke and no second-hand smoke. Other reasons participants like edibles included convenience, discreetness, longer-lasting highs, less intense highs, and edibles' ability to aid in relaxation and reduce anxiety more so than smoking marijuana. Concerns and dislikes about edibles included delayed effects, unexpected highs, the unpredictability of the high, and inconsistency of distribution of marijuana in the product. No participants in either location mentioned harmful health effects from consuming edibles as a concern'.

2017 Hamilton et al looked at the therapeutic use of cannabis among adults in Ontario. 'Data were derived from the 2013 and 2014 CAMH Monitor Survey of adults in Ontario, Canada. This repeated cross-sectional survey employed a regionally stratified design and utilized computer-assisted telephone interviewing. Analyses were based on 401 respondents who reported using cannabis.
The data indicated that 28.8% of those who used cannabis in the past year self-reported using cannabis for therapeutic purposes. Of therapeutic users, 15.2% reported having medical approval to use cannabis for therapeutic purposes. Cannabis use for therapeutic purposes was associated with more frequent use of cannabis, a moderate to high risk of problematic cannabis use, and a greater likelihood of using prescription opioids for medical purposes. There was little difference in cannabis use for therapeutic purposes according to sex, age, and marital status after adjusting for opioid use and problematic cannabis use'.

2017 Colorado: Impact of cannabis legalisation. Accounts of increased traffic fatalities, crimes, emergency department admissions, usage among young and older people , flourishing of the black market etc. all contained in 5 volumes to date from The Rocky Mountain High Intensity Trafficking Area.

2017 Meehan-Atrash et al found toxicants in dabbing. Dabbing consists of placing a small amount of cannabis extract -- a dab -- on a heated surface and inhaling the resulting vapour The team analyzed the chemical profile of terpenes -- the fragrant oils in marijuana and other plants -- by vaporizing them in much the same way as a user would vaporize hash oil. The dabbing experiments produced benzene -- a known carcinogen -- at levels many times higher than the ambient air. It also produced high levels of methacrolein, a chemical similar to acrolein, another carcinogen.

2017 Hauser et al looked at cannabinoids in pain management and palliative medicine. 'Of the 750 publications identified, 11 SRs met the inclusion criteria; 3 of them were of high and 8 of moderate methodological quality. 2 prospective long-term observational studies with medical cannabis and 1 with tetrahydrocannabinol/cannabidiol spray (THC/CBD spray) were also analyzed. There is limited evidence for a benefit of THC/CBD spray in the treatment of neuropathic pain. There is inadequate evidence for any benefit of cannabinoids (dronabinol, nabilone, medical cannabis, or THC/CBD spray) to treat cancer pain, pain of rheumatic or gastrointestinal origin, or anorexia in cancer or AIDS. Treatment with cannabis-based medicines is associated with central nervous and psychiatric side effects.The public perception of the efficacy, tolerability, and safety of cannabis-based medicines in pain management and palliative medicine conflicts with the findings of systematic reviews and prospective observational studies conducted according to the standards of evidence-based medicine.

2017 Meir investigated the assocaiations between butane hash oil (BHO) use and cannabis-related problems. A sample of 821 college students were recruited to complete a survey about their health and behavior. Participants who had used cannabis in the past year (33%, n=273) completed questions about their cannabis use, including their use of BHO and cannabis-related problems in eight domains: physical dependence, impaired control, academic-occupational problems, social-interpersonal problems, self-care problems, self-perception, risk behavior, and blackouts.Approximately 44% (n=121) of past-year cannabis users had used BHO in the past year. More frequent BHO use was associated with higher levels of physical dependence (RR=1.8), impaired control (RR=1.3), cannabis-related academic/occupational problems (RR=1.5) poor self-care (RR=1.3), and cannabis-related risk behavior (RR=1.2). After accounting for sociodemographic factors, age of onset of cannabis use, sensation seeking, overall frequency of cannabis use, and frequency of other substance use, BHO use was still associated with higher levels of physical dependence (RR=1.2).BHO use is associated with greater physiological dependence on cannabis, even after accounting for potential confounders. Longitudinal research is needed to determine if cannabis users with

higher levels of physiological dependence seek out BHO and/or if BHO use increases risk for physiological dependence.

2017 Guttmannova et al assessed the association between regular marijuana use and adult mental health outcomes. The present study is a prospective examination of the relationship between regular marijuana use from adolescence through young adulthood and mental health outcomes at age 33.Data came from a gender-balanced, ethnically diverse longitudinal panel of 808 participants from Seattle, Washington. Outcomes included symptom counts for six mental health disorders. Regular marijuana use was tracked during adolescence and young adulthood. Regression analyses controlled for demographics and early environment, behaviors, and individual risk factors.Nonusers of marijuana reported fewer symptoms of alcohol use disorder, nicotine dependence, and generalized anxiety disorder than any category of marijuana users. More persistent regular marijuana use in young adulthood was positively related to more symptoms of cannabis use disorder, alcohol use disorder, and nicotine dependence at age 33.Findings highlight the importance of avoiding regular marijuana use, especially chronic use in young adulthood. Comprehensive prevention and intervention efforts focusing on marijuana and other substance use might be particularly important in the context of recent legalization of recreational marijuana use in Washington and other U.S. states.

2017 Merlo et al looked at the gender differences in substance use and psychiatric distress among medical students. 'Medical students from all 9 medical schools in the state of Florida were invited via e-mail and/or announcements to complete an anonymous online questionnaire assessing their well-being. Of 5053 matriculating medical students, 1137 (57.1% female) responded to the questionnaire. Descriptive statistics, t tests, and chi-square analyses were computed using SPSS 20.Over 70% of students acknowledged binge drinking, with men reporting higher frequency than women ($\chi 2 = 13.90$, P = .003), and 22.7% (n = 201) reported marijuana use during medical school, with higher rates ($\chi 2 = 9.50$, P = .02) among men (27.0%, n = 99) than women (18.9%, n = 93). A significant minority of students reported nonmedical use of prescription stimulants and prescription opioids. In addition, 3.3% of male students (n = 12) compared with 0.6% of female students (n = 3) reported problematic drug use. Further, almost 2/3 of respondents reported decreased psychological health since beginning medical school, with women noting greater reductions ($\chi 2 = 12.39$, P = .05) and higher levels of stress ($\chi 2 = 16.30$, P = .003). Over 10% of students (n = 102) endorsed "thoughts of committing suicide" during medical school, and 70.1% felt they would benefit from mental healthcare (79.3% of women vs. 59.6% of men; $\chi 2 = 41.94$, P < .001), although only 39.8% accessed help'.

2017 Romero-Sandoval looked at cannabis and cannabinoids for chronic pain. We found that inhaled (smoked or vaporized) cannabis is consistently effective in reducing chronic non-cancer pain. Oral cannabinoids seem to improve some aspects of chronic pain (sleep and general quality of life), or cancer chronic pain, but they do not seem effective in acute postoperative pain, abdominal chronic pain, or rheumatoid pain. The available literature shows that inhaled cannabis seems to be more tolerable and predictable than oral cannabinoids. Cannabis or cannabinoids are not universally effective for pain. Continued research on cannabis constituents and improving bioavailability for oral cannabinoids is needed. Other aspects of pain management in patients using cannabis require further open discussion: concomitant opioid use, medical vs. recreational cannabis, abuse potential, etc.

2017 'Wong et al investigated medical cannabinoids in children and adolescents. Searching identified 2743 citations, and 103 full texts were reviewed. Searching identified 21 articles that met inclusion criteria, including 22 studies with a total sample of 795 participants. Five randomized controlled trials, 5 retrospective chart reviews, 5 case reports, 4 open-label trials, 2 parent surveys, and 1 case series were identified. Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, with increasing evidence of benefit for epilepsy. At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, and Tourette syndrome. The methodological quality of studies varied, with the majority of studies lacking control groups, limited by small sample size, and not designed to test for the statistical significance of outcome measures. Studies were heterogeneous in the cannabinoid composition and dosage and lacked long-term follow-up to identify potential adverse effects. Additional research is needed to evaluate the potential role of medical cannabinoids in children and adolescents, especially given increasing accessibility from state legalization and potential psychiatric and neurocognitive adverse effects identified from studies of recreational cannabis use'.

2017 Wang et al found that second-hand marijuana smoke impairs vascular endothelium function. 'Despite public awareness that tobacco second-hand smoke (SHS) is harmful, many people still assume that marijuana SHS is benign. Debates about whether smoke‐free laws should include marijuana are becoming increasingly widespread as marijuana is legalized and the cannabis industry grows. Lack of evidence for marijuana SHS causing acute cardiovascular harm is frequently mistaken for evidence that it is harmless,

despite chemical and physical similarity between marijuana and tobacco smoke. We investigated whether brief exposure to marijuana SHS causes acute vascular endothelial dysfunction.We measured endothelial function as femoral artery flow‐mediated dilation (FMD) in rats before and after exposure to marijuana SHS at levels similar to real‐world tobacco SHS conditions. One minute of exposure to marijuana SHS impaired FMD to a comparable extent as impairment from equal concentrations of tobacco SHS, but recovery was considerably slower for marijuana. Exposure to marijuana SHS directly caused cannabinoid‐independent vasodilation that subsided within 25 minutes, whereas FMD remained impaired for at least 90 minutes. Impairment occurred even when marijuana lacked cannabinoids and rolling paper was omitted. Endothelium‐independent vasodilation by nitroglycerin administration was not impaired. FMD was not impaired by exposure to chamber air. One minute of exposure to marijuana SHS substantially impairs endothelial function in rats for at least 90 minutes, considerably longer than comparable impairment by tobacco SHS. Impairment of FMD does not require cannabinoids, nicotine, or rolling paper smoke. Our findings in rats suggest that SHS can exert similar adverse cardiovascular effects regardless of whether it is from tobacco or marijuana'.

2017 NIDA National Institute of Drug Abuse (USA) September 2017 found that young adults' daily use of marijuana was causing concern. The 2016 drug use data among college/non-college age adults (19-22) was now available**.** Daily marijuana use is at the highest level since the early 1980s for this age group (7.8%), reaching the highest level seen for non-college youth (12.8%) and among the highest for full-time college students (4.9%).

2017 Harari et al found that teens who drank or smoked marijuana heavily are less likely to marry, go to college, or work full time**. '**Researchers examined data from the Collaborative Study on the Genetics of Alcoholism (COGA) to track the effect teenage alcohol and marijuana use has on the achievement of life goals, defined as educational achievement, full time employment, marriage and social economic potential. The study includes 1,165 young adults from across the United States whose habits were first assessed at age 12 and then at two-year intervals until they were between 25 and 34 years old. Most of the study participants had an alcoholic grandparent, parent, aunt or uncle. Overall, individuals who were dependent on either marijuana or alcohol during their teen years achieved lower levels of education, were less likely to be employed full time, were less likely to get married and had lower social economic potential. "This study found that chronic marijuana use in adolescence was negatively associated with achieving important developmental milestones in young adulthood. Awareness of marijuana's potentially deleterious effects will be important moving forward, given the current move in the US toward marijuana legalization for medicinal and possibly recreational use," said study author Elizabeth Harari. The researchers also found that dependence may have a more severe effect on young men. Dependent young men achieved less across all four measures, while dependent women were less likely than non-dependent women to obtain a college degree and had lower social economic potential, but were equally likely to get married or obtain full time employment. Previous research had shown that heavy use of alcohol or marijuana in adolescence affects people developmentally. This study followed up on that, to look at what happens after age 18. The life outcomes seem to show the differences are meaningful into adulthood'.

2017 Delteil et al looked at a case of death by self-mutilation after oral cannabis consumption. Abstract: Major self-mutilation (amputation, castration, self-inflicted eye injuries) is frequently associated with psychiatric disorders and/or substance abuse. A 35-year-old man presented with behavioral disturbances of sudden onset after oral cannabis consumption and major self-mutilation (attempted amputation of the right arm, self-enucleation of both eyes and impalement) which resulted in death. During the enquiry, four fragments of a substance resembling cannabis resin were seized at the victim's home. Autopsy confirmed that death was related to hemorrhage following the mutilations. Toxicological findings showed cannabinoids in femoral blood (tetrahydrocannabinol (THC) 13.5 ng/mL, 11-hydroxy-tetrahydrocannabinol (11-OH-THC) 4.1 ng/mL, 11-nor-9-carboxy-THC (THC-COOH) 14.7 ng/mL, cannabidiol (CBD) 1.3 ng/mL, cannabinol (CBN) 0.7 ng/mL). Cannabinoid concentrations in hair (1.5 cm brown hair strand/1 segment) were consistent with concentrations measured in chronic users (THC 137 pg/mg, 11-OH-THC 1 pg/mg, CBD 9 pg/mg, CBN 94 pg/mg). Analysis of the fragments seized confirmed that this was cannabis resin with high levels of THC (31-35%).

2017 Min et al found that **m**arijuana use is associated with hypersensitivity to multiple allergens in US adults.

A total of 2671 adults (aged 20-59 years) who participated in the 2005-2006 National Health and Nutrition Examination Survey were included. Participants completed a questionnaire on marijuana use and underwent sensitization tests to 19 specific allergens. Those who reported marijuana use for at least 1 day in the past 30 days were considered marijuana users.No difference was found in the history of allergy between

marijuana users and non-users. Compared with marijuana non-users as a reference group, the adjusted odds ratio (AOR) of sensitization to a specific allergen among marijuana users was significantly greater for antibodies against the following: Alternaria alternate, D. farinae, D. pteronyssin, ragweed, ryegrass, Bermuda grass, oak, birch, peanut, and cat dander. We suggest that marijuana use is associated with sensitization to specific allergens, including molds, dust mites, plants, and cat dander.

2017 Rusby et al looked at the legalization of recreational marijuana and community sales policy in Oregon and the impact on adolescent willingness and intent to use, parent use, and adolescent use. Studies investigating the impact of medical marijuana legalization have found no significant changes in adolescent use. In one of the few studies focused on recreational marijuana, we investigated how recreational marijuana legalization and community sales policy influenced factors that likely impact youth use (youth willingness and intent to use, parent use) as well as youth use. Legalization of recreational marijuana in Oregon coincided with our study on adolescent substance use. Cohort 1 transitioned from 8th to 9th grade prior to legalization and Cohort 2 made this transition during legalization (N = 444; 53% female). Communities were allowed to opt out of sales. Multivariate linear regression models estimated the impact of legalization and community sales policy on changes in attitudes and parent use (2 time points 1 year apart). Zero-inflated Poisson growth curve models estimated the effects on initial levels and rate of change from 8th through 9th grade (4 time points). In communities opting out of sales, the prior-to-legalization cohort was less likely to increase their willingness and intent to use marijuana, and the legalization cohort was more likely to increase intent to use. For youth who used marijuana, legalization was associated with increased use, and those in communities opting out of sales had greater growth in marijuana use. Community policy appears to impact youth attitudes toward, and use of, marijuana. Results suggest that legalization of recreational marijuana did not increase marijuana use for youth who did not use marijuana but did increase use in youth who were already using.

2017 Phillips et al looked at Marijuana use and associated motives in Colorado university students. College students (N = 300; 61% female) were recruited through introductory psychology courses and completed a series of questionnaires and a marijuana urine screen. Almost three-fourths of the sample reported lifetime use of marijuana. Sixty-five percent used marijuana within the last year and 29% tested positive on the urine screen. Hurdle Poisson regression models with a subset of participants (n = 117) showed non-Greek and freshman status were associated with increased number of days participants used marijuana in the last month. Problem marijuana use was positively associated with a range of motives-of note-motives focused on coping, boredom, alcohol, and food. Prevalence rates of marijuana use were high in this sample of college students in a state with legal recreational marijuana use.

2017 Druet et al investigated cannabis and cross allergy with food. ‘Cannabis use has increased over the last decade. At the same time, we see cannabis allergies appearing, ranging from simple rhinoconjunctivitis to anaphylactic-type reactions, some of which are severe since fatal cases have been described, but we also see allergic-induced food allergies cross-linked in the family of lipid transfer proteins (LTP). Indeed, cannabis contains an LTP called Can s 3. The LT are very widespread in the vegetable kingdom and are present in many vegetables and fruits. LTPs have a similar chemical structure and therefore cross-allergy is common. Thus, by becoming aware of the LTP of cannabis, it is possible to become allergic by a mechanism of cross-allergy to the other LTPs present in fruits and vegetables. This syndrome is referred to as cannabis-fruit-vegetable syndrome’.

2017 Kerr et al looked at Changes in undergraduates' marijuana, heavy alcohol and cigarette use following legalization of recreational marijuana use in Oregon. Repeated cross-sectional survey data from the 2012-16 administrations of the Healthy Minds Study was used from seven four-year universities in The United States. There were 10 924 undergraduate participants. One large public Oregon university participated in 2014 and 2016 (n = 588 and 1115, respectively); six universities in US states where recreational marijuana use was illegal participated both in 2016 and at least once between 2012 and 2015. Rates of marijuana use increased from pre- to post-2015 at six of the seven universities, a trend that was significant overall. Increases in rates of marijuana use were significantly greater in Oregon than in comparison institutions, but only among students reporting recent heavy alcohol use.Rates of Oregon college students' marijuana use increased (relative to that of students in other states) following recreational marijuana legislation in 2015, but only for those who reported recent heavy use of alcohol.

2017 Terry-McElrath et al looked at time-varying associations between perceived risk and marijuana use among US 12th grade students from 1991 to 2016. Self-reported data on past 12-month marijuana use, perceived risk of regular marijuana use, gender, and race/ethnicity were obtained from 275,768 US 12th grade students participating in the nationally representative Monitoring the Future study. Both before and after controlling for gender and race/ethnicity, perceived risk was a strong protective factor against adolescent marijuana use. The magnitude of the great risk/use association strengthened for Hispanic

students; remained generally stable over time for 12th graders overall, males, females, and White students; and weakened for Black students. The magnitude of the moderate risk/use association strengthened for 12th graders overall, males, females, White and Hispanic students, but did not continue to strengthen for Black students from 2005 onwards. In general, marijuana use prevalence decreased over time within all levels of perceived risk. Perceived risk remains a strong protective factor for adolescent marijuana use, and the protective association for moderate risk (vs. no/slight risk) is actually increasing over time. Results suggest that accurate and credible information on the risks associated with marijuana use should remain a key component of prevention efforts.

2017 Arria et al looked at the prevalence and incidence of drug taking among college students. Participants (N = 1,253; 52% female) were young adults who were originally enrolled as first-time, first-year students at a university in the mid-Atlantic US. Annual personal interviews gathered data about the use of seven illicit drugs and three prescription drugs used nonmedically. Annual follow-up rates ranged from 76 to 91%. Marijuana was the most commonly used drug in every year of the study, with the highest annual prevalence estimates in Year 3 (47%wt). In Year 8, when the modal age of participants was 25, 29%wt used marijuana during the past year. Nonmedical use of prescription drugs was more prevalent during college than in the later years of the study. Although the prevalence of cocaine and ecstasy use was low (cumulative prevalence estimates of 17%wt and 13%wt, respectively), incidence for these drugs was particularly high in the later years of the study. Drug use is prevalent among college students, and drug use persists among young adults, even after many have graduated college.

2017 Holitzki et al looked at the health effects of exposure to second and third-hand marijuana smoke. ‘6 databases were searched from inception to October 2017. Studies were included if they were human, in vivo or in vitro studies with more than 1 case reported in English or French, and reported original, quantitative data. Three outcomes were extracted: 1) cannabinoids and cannabinoid metabolites in bodily fluids, 2) self-reported psychoactive effects and 3) eye irritation and discomfort. Of the 1701 abstracts identified, 60 proceeded to full-text review; the final data set contained 15 articles. All of the included studies were of good to poor quality as assessed with the Downs and Black checklist. There is evidence of a direct relation between the tetrahydrocannabinol content of marijuana and effects on those passively exposed. This relation is mediated by several environmental factors including the amount of smoke, ventilation, air volume, number of marijuana cigarettes lit and number of smokers present. No evidence was identified assessing exposure to third-hand marijuana smoke or the health effects of long-term exposure.

2017 Nappe et al investigated a pediatric death due to myocarditis after exposure to cannabis. Abstract: Since marijuana legalisation, pediatric exposures to cannabis have increased.To date, pediatric deaths from cannabis exposure have not been reported. The authors report an eleven month old male who, following cannabis exposure, presented with central nervous system depression after seizure, and progressed to cardiac arrest and died. Myocarditis was diagnosed post mortem and cannabis exposure was confirmed. Given the temporal relationship of these two rare occurencies – cannabis exposure and sudden death secondary to myocarditis in an 11-month old – as well as histological consistency with drug-induced myocarditis, without confirmed alternate causes, and prior reported cases of cannabis-associated myocarditis, a possible relationship exists between cannabis exposure in this child and myocarditis leading to death. In areas where cannabis is commercially available or decriminalised, the authors urge clinicians to preventively counsel parents and to include cannabis exposure in the differential diagnosisof patients pesenting with myocarditis.

2017 Olfson et al looked at cannabis use and the risk of prescription opioid use disorder in the United States. ‘The authors used logistic regression models to assess prospective associations between cannabis use at wave 1 (2001–2002) and nonmedical prescription opioid use and prescription opioid use disorder at wave 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions. Corresponding analyses were performed among adults with moderate or more severe pain and with nonmedical opioid use at wave 1. Cannabis and prescription opioid use were measured with a structured interview (the Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV version). Other covariates included age, sex, race/ethnicity, anxiety or mood disorders, family history of drug, alcohol, and behavioral problems, and, in opioid use disorder analyses, nonmedical opioid use. In logistic regression models, cannabis use at wave 1 was associated with increased incident nonmedical prescription opioid use (odds ratio=5.78) and opioid use disorder (odds ratio=7.76) at wave 2. These associations remained significant after adjustment for background characteristics (nonmedical opioid use: adjusted odds ratio=2.62, opioid use disorder: adjusted odds ratio=2.18). Among adults with pain at wave 1, cannabis use was also associated with increased incident nonmedical opioid use (adjusted odds ratio=2.99) at wave 2; it was also associated with increased incident prescription opioid use disorder, although the association fell

short of significance (adjusted odds ratio=2.14). Among adults with nonmedical opioid use at wave 1, cannabis use was also associated with an increase in nonmedical opioid use (adjusted odds ratio=3.13). Cannabis use appears to increase rather than decrease the risk of developing nonmedical prescription opioid use and opioid use disorder.

2017 Franklyn et al investigated the impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario. 'A retrospective cohort study was conducted using anonymized electronic medical records from 58 clinics offering opioid agonist therapy in Ontario, Canada. One-year treatment retention was the primary outcome of interest and was measured for patients who did and did not have a cannabis positive urine sample in their first month of treatment, and as a function of the proportion of cannabis-positive urine samples throughout treatment. Our cohort consisted of 644 patients, 328 of which were considered baseline cannabis users and 256 considered heavy users. Patients with baseline cannabis use and heavy cannabis use were at increased risk of dropout (38.9% and 48.1%, respectively). When evaluating these trends by gender, only female baseline users and male heavy users are at increased risk of premature dropout. Both baseline and heavy cannabis use are predictive of decreased treatment retention, and differences do exist between genders. With cannabis being legalized in the near future, physicians should closely monitor cannabis-using patients and provide education surrounding the potential harms of using cannabis while receiving treatment for opioid use disorder.

2017 Amato et al **c**onducted a **s**ystematic review of safeness and therapeutic efficacy of cannabis in patients with multiple sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy. Abstract: medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. In the United States, 23 states and Washington DC (May 2015) have introduced laws to permit the medical use of cannabis. Within the European Union, medicinal cannabis laws and praxis vary wildly between Countries. The aim was to provide evidence for benefits and harms of cannabis (including extracts and tinctures) treatment for adults in the following indications: control of spasticity and pain in patients with multiple sclerosis; control of pain in patients with chronic neuropathic pain; control of nausea and vomiting in adults with cancer receiving chemotherapy.we searched the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE from inception to September 2016. We also searched for on-going studies via ClinicalTrials.gov and the World Health Organization and International Clinical Trials Registry Platform (ICTRP) search portal. All searches included also non-English language literature. All relevant randomized controlled trials (RCTs) evaluating the safety and efficacy of cannabis (including extracts and tinctures) compared with placebo or other pharmacological agents were included. Three authors independently evaluated the titles and abstracts of studies identified in the literature searches for their eligibility. For studies considered eligible, we retrieved full texts. Three investigators independently extracted data. For the assessment of the quality of evidence, we used the standard methodological procedures recommended by Cochrane and GRADE working Group.41 trials (4,550 participants) were included; 15 studies considered efficacy and safety of cannabis for patients with multiple sclerosis, 12 for patients with chronic pain, and 14 for patients with cancer receiving chemotherapy. The included studies were published between 1975 and 2015, and the majority of them were conducted in Europe. We judged almost 50% of these studies to be at low risk of bias. The large majority (80%) of the comparisons were with placebo; only 8 studies included patients with cancer receiving chemotherapy comparing cannabis with other antiemetic drugs. Concerning the efficacy of cannabis (compared with placebo) in patients with multiple sclerosis, confidence in the estimate was high in favour of cannabis for spasticity (numerical rating scale and visual analogue scale, but not the Ashworth scale) and pain. For chronic and neuropathic pain (compared with placebo), there was evidence of a small effect; however, confidence in the estimate is low and these results could not be considered conclusive. There is uncertainty whether cannabis, including extracts and tinctures, compared with placebo or other antiemetic drugs reduces nausea and vomiting in patients with cancer requiring chemotherapy, although the confidence in the estimate of the effect was low or very low. In the included studies, many adverse events were reported and none of the studies assessed the development of abuse or dependence. There is incomplete evidence of the efficacy and safety of medical use of cannabis in the clinical contexts considered in this review. Furthermore, for many of the outcomes considered, the confidence in the estimate of the effect was again low or very low. To give conclusive answers to the efficacy and safety of cannabis used for medical purposes in the clinical contexts considered, further studies are needed, with higher quality, larger sample sizes, and possibly using the same diagnostic tools for evaluating outcomes of interest.

2017 Patrick looked at patterns of simultaneous and concurrent alcohol and marijuana use among adolescents. 'Data from US-national samples of 12th graders (N = 84,805, 48.4% female) who participated in the Monitoring the Future study from 1976 to 2016 and who used alcohol and/or marijuana in the past

12 months were used to identify latent classes of alcohol use, marijuana use, and simultaneous alcohol and marijuana (SAM) use. A four-class solution indicated four patterns of use among adolescents: (1) Simultaneous alcohol and marijuana (SAM) use with binge drinking and recent marijuana use (SAM-Heavier Use; 11.2%); (2) SAM use without binge drinking and with recent marijuana use (SAM-Lighter Use; 21.6%); (3) Marijuana use and alcohol use but no SAM use (Concurrent Use; 10.7%); and (4) Alcohol use but no marijuana or SAM use (Alcohol-Only Use; 56.4%). Membership in either SAM use class was associated with a higher likelihood of truancy, evenings out, and use of illicit drugs other than marijuana. SAM-Heavier Use, compared to SAM-Lighter Use, class members were more likely to report these behaviors and be male, and less likely to have college plans'.

2017 Drouet et al loked at cannabis and crossed allergy with food. Abstract:'Cannabis use has increased over the last decade. At the same time, we see cannabis allergies appearing, ranging from simple rhinoconjunctivitis to anaphylactic-type reactions, some of which are severe since fatal cases have been described, but we also see allergic-induced food allergies cross-linked in the family of lipid transfer proteins (LTP). Indeed, cannabis contains an LTP called Can s 3. The LT are very widespread in the vegetable kingdom and are present in many vegetables and fruits. LTPs have a similar chemical structure and therefore cross-allergy is common. Thus, by becoming aware of the LTP of cannabis, it is possible to become allergic by a mechanism of cross-allergy to the other LTPs present in fruits and vegetables. This syndrome is referred to as cannabis-fruit-vegetable syndrome'.

2017 Borodovsky et al legal cannabis laws, home cultivation and use of edible cannabis products. Abstract: 'Over half of U.S. states have enacted legal cannabis laws (LCL). In parallel, edible cannabis products (i.e., edibles) have presented new regulatory challenges. LCL provisions that dictate access to cannabis (e.g., home cultivation (HC) or dispensaries (DSP)) may impact edible production and use. This study examined relationships among HC and DSP provisions, cannabis cultivation, and edible use. An online cannabis use survey was distributed using Facebook. Data were collected from 1813 cannabis-using adults. U.S. states were classified as states without LCL (Non-LCL) or LCL states that: (1) only permit DSP (LCL DSP-only), (2) only permit HC (LCL HC-only), or (3) permit HC and DSP (LCL HC+DSP). Analyses tested associations among these classifications, cannabis growing, and edible use and procurement. Individuals in LCL HC-only and LCL HC+DSP states were more likely to report currently growing cannabis at home (OR: 3.3, OR: 3.9, respectively) and past-month edible use (OR: 2.1, OR: 2.9, respectively) than individuals in LCL DSP-only states. Regardless of state, those who had grown cannabis were more likely to have made edibles than those who had never grown cannabis (OR: 2.2). Individuals in LCL HC-only states were more likely to have made edibles in the past month than individuals from Non-LCL (OR: 2.75) and DSP-only states (OR: 2.1), Individuals in LCL HC+DSP states were more likely to have purchased edibles in the past month than individuals from Non-LCL (OR: 3.7) and DSP-only states (OR: 3.2).Specific LCL provisions may differentially affect individuals' propensity to grow cannabis and make, buy, and use edible cannabis products. Permitting home cultivation contributes to a greater likelihood of growing cannabis. Those who grow cannabis economize the plant by creating homemade edible cannabis products. Conversely, permitting dispensaries increases the likelihood of purchasing edibles. The psychoactive effects of edibles with unknown and variable cannabinoid content will be unpredictable. Policymakers should carefully consider how specific LCL provisions can affect patterns of cannabis edible product access and quality.

2017 Beaulieu investigated the anesthetic implications on recreational drug use. 'Addicted patients may present for anesthetic care in a variety of circumstances in everyday elective surgeries or in acute or life-saving situations, such as emergency Cesarean delivery or trauma surgery. Therefore, it is important for anesthesiologists to know about the most common illicit drugs being used, their clinical presentation and side effects, and the anesthetic options that are beneficial or detrimental to these patients. The most frequently used illicit substances, apart from alcohol and tobacco, are cannabis, cocaine, heroin, prescription opioids, methamphetamine, and hallucinogens. When planning anesthetic care, it is important for anesthesiologists to understand the effects of these agents, including various drug interactions, to predict tolerance to some anesthetic agents, to recognize drug withdrawal signs and symptoms, and to be prepared to manage all these factors in the perioperative period'.

2017 Hasin looked at the epidemiology of cannabis use and associated problems. Abstract: 'This review provides an overview of the changing US epidemiology of cannabis use and associated problems. Adults and adolescents increasingly view cannabis as harmless, and some can use cannabis without harm. However, potential problems include harms from prenatal exposure and unintentional childhood exposure; decline in educational or occupational functioning after early adolescent use, and in adulthood, impaired driving and vehicle crashes; cannabis use disorders (CUD), cannabis withdrawal, and psychiatric comorbidity. Evidence suggests national increases in cannabis potency, prenatal and unintentional childhood exposure; and in adults, increased use, CUD, cannabis-related emergency room visits, and fatal

vehicle crashes. Twenty-nine states have medical marijuana laws (MMLs) and of these, 8 have recreational marijuana laws (RMLs). Many studies indicate that MMLs or their specific provisions did not increase adolescent cannabis use. However, the more limited literature suggests that MMLs have led to increased cannabis potency, unintentional childhood exposures, adult cannabis use,and adult CUD. Ecological-level studies suggest that MMLs have led to substitution of cannabis for opioids, and also possiblyfor psychiatric medications. Much remains to be determined about cannabis trends and the role of MMLs and RMLs in these trends. The public, health professionals, and policy makers would benefit from education about the risks of cannabis use, the increases in such risks, and the role of marijuana laws in these increases'.

2017 Szutorisz et al looked at the epigenetic issues to do with cannabis (epigenic imprint and legacy on brain and behaviour). Abstract: 'Extensive debates continue regarding marijuana (Cannabis spp), the most commonly used illicit substance in many countries worldwide. There has been an exponential increase of cannabis studies over the past two decades but the drug's long-term effects still lack in-depth scientific data. The epigenome is a critical molecular machinery with the capacity to maintain persistent alterations of gene expression and behaviors induced by cannabinoids that have been observed across the individual's lifespan and even into the subsequent generation. Though mechanistic investigations regarding the consequences of developmental cannabis exposure remain sparse, human and animal studies have begun to reveal specific epigenetic disruptions in the brain and the periphery. In this article, we focus attention on long-term disturbances in epigenetic regulation in relation to prenatal, adolescent and parental germline cannabinoid exposure. Expanding knowledge about the protracted molecular memory could help to identify novel targets to develop preventive strategies and treatments for behaviors relevant to neuropsychiatric risks associated with developmental cannabis exposure.

2017 Chinello et al looked at canabinoid poisoning by hemp seed oil in a child. Abstract: We report a case of mild cannabinoid poisoning in a preschool child, after 3-week ingestion of hemp seed oil prescribed by his pediatrician to strengthen his immune system. The patient presented neurological symptoms that disappeared after intravenous hydration. A possible mild withdrawal syndrome was reported after discharge. The main metabolite of Δ-tetrahydrocannabinol was detected in urine, and very low concentration of Δ-tetrahydrocannabinol was detected in the ingested product. This is, as far as we know, the first report of cannabinoid poisoning after medical prescription of hemp seed oil in a preschool child.

2018 Shapiro et al looked at cryptococcal meningitis in a daily cannabis smoker without evidence of immunodeficiency. Cryptococcal meningitis is a life-threatening condition most commonly observed in immunocompromised individuals. We describe a daily cannabis smoker without evidence of immunodeficiency presenting with confirmed Cryptococcus neoformans meningitis. An investigation of cannabis samples from the patient's preferred dispensary demonstrated contamination with several varieties of Cryptococcus, including C. neoformans, and other opportunistic fungi. These findings raise concern regarding the safety of dispensary-grade cannabis, even in immunocompetent users.

2018 Nugent et al looked at patterns and correlates of medical cannabis use for pain among patients prescribed long-term opioid therapy**.** Abstract: Little is known about co-occurring long-term opioid therapy (LTOT) and medical cannabis use. We compared characteristics of patients prescribed LTOT who endorsed using medical cannabis for pain to patients who did not report cannabis use. Participants (n=371) prescribed LTOT completed self-report measures about pain, substance use, and mental health. Eighteen percent of participants endorsed using medical cannabis for pain. No significant differences were detected on pain-related variables, depression, or anxiety between those who endorsed medical cannabis use and those who did not. Medical cannabis users had higher scores of risk for prescription opioid misuse (median=17.0 vs. 11.5, $p<0.001$), rates of hazardous alcohol use (25% vs. 16%, $p<0.05$), and rates of nicotine use (42% vs. 26%, $p=0.01$). Multivariable analyses indicated that medical cannabis use was significantly associated with risk of prescription opioid misuse ($\beta=0.17$, $p=0.001$), but not hazardous alcohol use (aOR=1.96, 95% CI=0.96-4.00, $p=0.06$) or nicotine use (aOR=1.61, 95% CI=0.90-2.88, $p=0.11$). There are potential risks associated with co-occurring LTOT and medical cannabis for pain. Study findings highlight the need for further clinical evaluation in this population. Future research is needed to examine the longitudinal impact of medical cannabis use on pain-related and substance use outcomes.

2018 Potter et al looked at the potency of THC and other cannabinoids in cannabis in 2016. Abstract: In 2005 and 2008, studies reported that cannabis in England had become dominated by the sinsemilla (unseeded female) form. The average potency (Δ9 -tetrahydrocannabinol [THC] content) of this material had doubled over the previous decade. Cannabis resin then circulating contained approximately equal ratios of THC and cannabidiol (CBD), whereas sinsemilla was almost devoid of CBD. Despite raised health concerns regarding sinsemilla use and the development of psychotic disorders, no update on street cannabis

potency has been published since 2008. A total of 995 seized cannabis samples were acquired from the same 5 constabulary areas included in the 2005 study. The differing forms were segregated, and a representative 460 samples analyzed to assess their cannabinoid content using gas chromatography. The resultant median sinsemilla potency of 14.2% THC was similar to that observed in 2005 (13.9%). In each case, sinsemilla contained minimal CBD. Compared with 2005, resin had significantly higher mean THC (6.3%) and lower CBD (2.3%) contents ($p < 0.0001$). Although the average THC concentration in sinsemilla samples across the 5 constabularies has remained stable since 2005, the availability of this potent form of cannabis has further increased. Moreover, the now rarer resin samples show significantly decreased CBD contents and CBD:THC ratios, leaving the United Kingdom's cannabis street market populated by high-potency varieties of cannabis, which may have concerning implications for public health.

2018 Kelly et al looked at recovery from cannabis problems compared with other drugs.
Abstract: 9.1% of the US adult population reported resolving a significant substance problem, and of these, 10.97% were CAN. Compared to ALC ($M = 49.79$) or OTH ($M = 43.80$), CAN were significantly younger ($M = 39.41$, $p < 0.01$), had the earliest onset of regular use (CAN $M = 16.89$, ALC $M = 19.02$, OTH $M = 23.29$, $p < 0.01$), and resolved their problem significantly earlier (CAN $M = 28.87$, ALC $M = 37.86$, OTH $M = 33.06$, $p < 0.01$). Compared to both ALC and OTH, CAN were significantly less likely to report use of inpatient treatment and used substantially less outpatient treatment, overall ($p < 0.01$), although CAN resolving problems more recently were more likely to have used outpatient treatment ($p < 0.01$). Lifetime attendance at mutual-help meetings (e.g., AA) was similar, but CAN ($M = 1.67$) had substantially lower recent attendance compared to ALC ($M = 7.70$) and OTH ($M = 7.65$). QOL indices were similar across groups.Approximately 2.4 million Americans have resolved a significant cannabis problem. Compared to ALC and OTH, the pattern of findings for CAN suggest similarities but also some notable differences in characteristics and problem resolution pathways particularly regarding earlier problem offset and less use of formal and informal services. Within a shifting policy landscape, research is needed to understand how increases in population exposure and potency may affect the nature and magnitude of differences observed in this preliminary study.

2018 NIDA produced a general information paper - What are the effects of secondhand exposure to marijuana smoke? Ref: https://www.drugabuse.gov/publications/marijuana/what-are-effects-secondhand-exposure-to-marijuana-smoke References to specific papers are given in this link.

2018 Weinberger looked at cannabis use and increased risk of cigarette smoking, initiation, persistence and relapse. Abstract: Analyses included respondents who completed Waves 1 (2001-2002) and 2 (2004-2005) of the National Epidemiologic Survey on Alcohol and Related Conditions and responded to questions about cannabis use and smoking status (n = 34,639). Multivariable logistic regression models were used to calculate the odds of cigarette use at Wave 2 among Wave 1 daily smokers, nondaily smokers, former smokers, and nonsmokers by Wave 1 cannabis use. In unadjusted analyses, Wave 1 cannabis use was associated with increased odds of Wave 2 daily and nondaily smoking for Wave 1 nonsmokers (daily OR = 2.90; 95% CI, 2.10-4.00; nondaily OR = 4.45; 95% CI, 3.97-5.00) and Wave 2 relapse to daily and nondaily smoking for Wave 1 former smokers (daily OR = 4.18, 95% CI, 3.01-5.81; nondaily OR = 5.24; 95% CI, 3.74-7.34). Wave 1 cannabis use was associated with decreased odds of Wave 2 smoking cessation for Wave 1 daily cigarette smokers (OR = 0.57; 95% CI, 0.51-0.64). The associations remained significant for daily smoking initiation (OR = 1.43; 95% CI, 1.06-1.93), daily smoking relapse (OR = 1.47; 95% CI, 1.00-2.16), and smoking cessation (OR = 0.77; 95% CI, 0.69-0.87) after adjusting for demographics and psychiatric disorders. Associations remained significant for nondaily smoking initiation (OR = 1.85; 95% CI, 1.59-2.16) and nondaily smoking relapse (OR = 1.63; 95% CI, 1.05-2.54) after adjusting for these covariates as well as for alcohol and substance use disorders. Cannabis use was associated with increased initiation of, persistence of, and relapse to cigarette smoking.

JAMA 2 Papers on legal medical cannabis and decline of opiod use in USA April 2018 and 'Invited Comment' on subject Aprl 2018

A slew of news articles flooded the print, broadcast, and internet media this week about two new studies published in Monday's online issue of *JAMA Internal Medicine*. One study found that states with medical marijuana laws are associated with reductions in Medicare Part D opioid prescriptions, compared to states that do not have such laws. The other found a similar association in states with both medical and recreational marijuana laws in the Medicaid population. Lead author of the first study is David Bradford, PhD, at the School of Public and International Affairs of the University of Georgia. UGA sent out a press release promoting Dr. Bradford's study with this title: "SPIA Professor Pens New Study: Legalized Medical Cannabis Lowers Opioid Use."**Not quite.**

Dr. Bradford's study finds a correlation between states with medical marijuana laws and a reduction in opioid *prescriptions*, not use. And only in the *Medicare Part D population*, not the whole population. Dr. Bradford himself notes this when citing the study's limitations in his journal article. Yet many of the news stories picked up his

university's headline.
And he pushed this misinformation along in interviews he gave to the press, telling the Cox Media Group, "'There are substantial reductions in opiate use' in states that have initiated dispensaries for medical marijuana," when in fact there are significant reductions in opioid prescriptions rather than use.
Dr. Bradford also tells his interviewers that the 2017 National Academies of Sciences, Engineering, and Medicine (NAS) review of the marijuana literature found "conclusive evidence that there are benefits to cannabis for chronic pain in adults, for nausea associated with chemotherapy, and for spasticity and seizures." He doesn't understand that all of the evidence for the last three conditions and most of it for chronic pain came from randomized controlled trials of purified cannabinoids rather the kinds of marijuana states have legalized for medical use.
He tells AP reporter Malcolm Ritter that the NAS report presents evidence that is "hard to ignore" and therefore federal laws should be changed to allow doctors to prescribe marijuana for pain treatment.

An accompanying editorial in the journal by two physicians not affiliated with these studies notes that other studies find legal marijuana *increases* opioid use. They warn than marijuana policy has gotten far ahead of marijuana science and we must remedy this quickly.
Perhaps people with chronic pain will get more relief from purified cannabinoids than opioids, but we won't know that until randomized, controlled trials are conducted to find out if that's true. At best, ecological studies like the two published this week can push us towards research, but certainly not policy.
Read Invited comment:"The Role of Cannabis Legalization in the Opioid Crisis"
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2676997 Hill et al
Read "Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population" Bradford et al
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2676999
Read "Association of Medical and Adult-Use Marijuana Laws With Opioid Prescribing for Medicaid Enrollees".
https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2677000 Wen et al

2018 Caputi et al investigated whether medical marijuana users were more likely to use prescription medicines. Abstract Objectives: Previous studies have found a negative population-level correlation between medical marijuana availability in US states, and trends in medical and nonmedical prescription drug use. These studies have been interpreted as evidence that use of medical marijuana reduces medical and nonmedical prescription drug use. This study evaluates whether medical marijuana use is a risk or protective factor for medical and nonmedical prescription drug use. Methods: Simulations based upon logistic regression analyses of data from the 2015 National Survey on Drug Use and Health were used to compute associations between medical marijuana use, and medical and nonmedical prescription drug use. Adjusted risk ratios (RRs) were computed with controls added for age, sex, race, health status, family income, and living in a state with legalized medical marijuana. Results: Medical marijuana users were significantly more likely (RR 1.62, 95% confidence interval [CI] 1.50-1.74) to report medical use of prescription drugs in the past 12 months. Individuals who used medical marijuana were also significantly more likely to report nonmedical use in the past 12 months of any prescription drug (RR 2.12, 95% CI 1.67-2.62), with elevated risks for pain relievers (RR 1.95, 95% CI 1.41-2.62), stimulants (RR 1.86, 95% CI 1.09-3.02), and tranquilizers (RR 2.18, 95% CI 1.45-3.16). Conclusions: Our findings disconfirm the hypothesis that a population-level negative correlation between medical marijuana use and prescription drug harms occurs because medical marijuana users are less likely to use prescription drugs, either medically or nonmedically. Medical marijuana users should be a target population in efforts to combat nonmedical prescription drug use.
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2018 Caputi et al Looked at the numbers of Americans who seek and find illicit marijuana online. To observe the online marijuana market place, Google searches in the US between January 2005 and June 2017 that included the words marijuana, weed, pot, cannabis combined with terms such as buy, shop or order, were carried out. They found that shopping searches nearly tripled in the US from 2005 to 2017, peaking between 1.4 million and 2.4 million each month. Highest numbers of searches were found in Washington, Oregon, Colorado and Nevada. The annual growth rate in searching for these terms increased in all but 2 states, Alabama and Mississippi. Three out of every four searches resulted in a mail-order marijuana retailer as the very first suggested link. Anyone, of any age can buy marijuana from their smartphone wherever they live.

2018 Vo et al looked at the dangers of eating edibles containg THC. Twelve children and 9 adults were identified, with 16 patients having detectable serum THC and THC metabolites. All patients presented to hospitals with a variety of constitutional symptoms and all were discharged home within 12 hours. In general, pediatric patients had more severe symptoms and longer hospital length of stay, and, uniquely, a majority presented with leukocytosis and elevated lactic acid levels. We recommend that efforts be made to increase general public awareness in regard to the potential hazards of THC-containing edibles resembling commercially available food products.

2018 Dai et al investigated electronic cigarettes and future marijuana use. Absract: Youth (aged 12‐17 years) never marijuana users at wave 1 (n = 10 364; 2013‐2014) from the Population Assessment of Tobacco and Health study were followed-up in 1 year (wave 2, 2014‐2015). Multivariable logistic regressions were performed to evaluate associations between e-cigarette use at wave 1 and ever/heavy marijuana use in the past 12 months (P12M) and at wave 2. Among never marijuana users, e-cigarette ever use (versus never use) at wave 1 was associated with increased likelihood of marijuana P12M use (adjusted odds ratio [aOR] = 1.9; 95% confidence interval [CI]: 1.4‐2.5) at wave 2. There was a significant interaction between e-cigarette use and age (P < .05) with aOR = 2.7 (95% CI: 1.7‐4.3) for adolescents aged 12 to 14 and aOR = 1.6 (95% CI: 1.2‐2.3) for adolescents aged 15 to 17. The association with heavy marijuana use was significant among younger adolescents (aOR = 2.5; 95% CI: 1.2‐5.3) but was not among older adolescents. Heavier e-cigarette use at wave 1 yielded higher odds of P12M and heavy marijuana use at wave 2 for younger adolescents. E-cigarette use predicts subsequent marijuana use among youth, with a stronger associations among young adolescents. Reducing youth access to e-cigarettes may decrease downstream marijuana use.

2018 Kenne et al looked at the use of substances other than nicotine in electronic cigarettes among college students. Absract: Cross-sectional data from 1542 undergraduate college student e-cigarette users from a large Midwestern university were collected via online survey to assess prevalence of e-cigarette use, reasons for use, perceived harm, and prevalence and predictors of OSUE (Other Substance Use in E-Cigarettes). Nearly 7% (6.94%) reported using an e-cigarette to vaporize and inhale a substance other than nicotine. Current tobacco cigarette smokers were significantly more likely to report OSUE (51.0%) as compared with never (33.7%) and former (15.4%) smokers. Among respondents reporting OSUE, the primary reason for e-cigarette use was “safer than cigarettes” (21.7%), followed by “experimentation” (18.9%) and “friends use” (17.0%). Most (77.9%) reported using cannabis or some derivative of cannabis in an e-cigarette. Binomial logistic regression found that women were less likely to report OSUE by a factor of 0.60, former tobacco cigarette smokers as compared with never smokers were more likely to report OSUE by a factor of 1.87, and e-cigarette users who reported using e-cigarettes for “cool or trendy” reasons were more likely to report OSUE by a factor of 2.89. Little is known regarding the health effects of cannabis and cannabis derivatives delivered through e-cigarettes. Concern may also be warranted regarding the potential dangers of this young population using substances more dangerous than cannabis in e-cigarettes. Knowledge is limited regarding the public health impact of vaping cannabis or other illicit substances among college student populations.

2018 Frohe et al looked for correlates of cannabis vape-pen use and knowledge among US college students. Abstract: The proliferation of electronic devices, such as vape-pens, has provided alternative means for cannabis use. Research has found cannabis-vaping (i.e., vape-pen use) is associated with lower perceived risks and higher cannabis use. Knowledge of these products may increase likelihood of subsequent use. As policies for cannabis shift, beliefs that peers and family approve of this substance use (injunctive norms) increase and there has been an increase in vape-pen use among young adults (18–35 year olds); however, correlates thereof remain unknown. Young adults often engage in cross-substance use with cannabis and alcohol, making alcohol a potential correlate of cannabis vape-pen use and knowledge. Therefore, we examined alcohol use and other potential correlates of vape-pen use and knowledge among a sample of university students. This secondary data analysis utilized surveys at multiple colleges in the U.S. (N = 270). Alcohol use, social anxiety, cannabis expectancies, injunctive and descriptive norms and facets of impulsivity were examined as correlates of vape-pen use and knowledge using bivariate correlations and logistic regressions.
Alcohol use was correlated with cannabis vape-pen use and knowledge. Frequency of cannabis use, peer injunctive norms, and positive expectancies were associated with increased likelihood of vape-pen use. Lack of premeditation, a facet of impulsivity, was associated with cannabis vape-pen knowledge.

2018 Wilhite et al investigated freshman year alcohol and marijuana use prospectively predict time to college graduation and subsequent adult roles and independence. Abstact: Participants were part of a longitudinal study that began in 2004. The first analyses focused on freshman year (N = 2,050). The second analyses corresponded to a subset of participants at age 27 (N = 575). Measures included self-reported substance use, adult role adoption, and university reported graduation dates. Results indicated that frequent binge drinking and marijuana use during freshman year predicted delayed college graduation. Those who took longer to graduate were more likely to have lower incomes and were less likely to obtain a graduate degree. Taking 5–6 years to graduate was associated with greater likelihood of alcohol-related problems.

2018 Pediatric Academic Societies Meeting looked at the correlation between second-hand marijuana and tobacco smoke exposure and children ED visits. The research included a cross-sectional survey of caregivers of children presenting to the ED of an urban, tertiary care, academic children's hospital in Colorado. Data collected included caregiver demographics and use of tobacco and/or marijuana, along with index child medical history, number of overall ED visits and number of tobacco sensitive conditions in the

prior year. Caregivers were classified into four categories depending on use: marijuana use only, tobacco use only, both tobacco and marijuana use, and neither marijuana nor tobacco use (control group). Poisson regression models were created to determine differences in overall ED visitation, as well as tobacco sensitive conditions. Results were expressed using incident rate ratios (IRR) and 95% confidence intervals. A total of 1,500 caregivers completed the survey. The survey found that overall, 140 caregivers (9.2 percent, 95%CI = 7.7-10.7 percent) reported regularly smoking marijuana, and 285 caregivers (19 percent, 17.1-21.1 percent) reported regularly smoking tobacco. Exposure groups included: marijuana only (n=62, 4.1 percent), tobacco only (n=213, 14.2 percent), marijuana and tobacco (n=75, 5percent), and unexposed (n=1147, 76.6 percent). When compared against each other, all groups had a similar rate of ED visitation other than the marijuana and tobacco group which had a significantly higher rate of ED visits compared to the controls. Children in the marijuana + tobacco group also had a statistically significant increase in otitis media episodes compared to controls (IRR = 1.81, 95%CI = 1.38, 2.35); differences were not elicited among the other groups or for other tobacco sensitive conditions

2018 Molina et al looked at substance use through adolescence into early adulthood after childhhod-diagnosed ADHD. Abstracxt: Five hundred forty-seven children, mean age 8.5, diagnosed with DSM-IV combined-type ADHD and 258 classmates without ADHD (local normative comparison group; LNCG) completed the Substance Use (SU) Questionnaire up to eight times from mean age 10 to mean age 25. In adulthood, weekly marijuana use (32.8% ADHD vs. 21.3% LNCG) and daily cigarette smoking (35.9% vs. 17.5%) were more prevalent in the ADHD group than the LNCG. The cumulative record also revealed more early substance users in adolescence for ADHD (57.9%) than LNCG (41.9%), including younger first use of alcohol, cigarettes, marijuana, and illicit drugs. Alcohol and non-marijuana illicit drug use escalated slightly faster in the ADHD group in early adolescence. Early SU predicted quicker SU escalation and more SU in adulthood for both groups. Frequent SU for young adults with childhood ADHD is accompanied by greater initial exposure at a young age and slightly faster progression. Early SU prevention and screening is critical before escalation to intractable levels.

2018 D'Amico et al investigated changes in exposure to medical marijuana advertising and subsequent adolescent marijuana use. Abstract: We followed two cohorts of 7th and 8th graders (mean age 13) recruited from school districts in Southern California from 2010 until 2017 (mean age 19) to examine effects of MM advertising on adolescents' marijuana use, cognitions, and consequences over seven years. Latent growth models examined trajectories of self-reported exposure to medical marijuana ads in the past three months and trajectories of use, cognitions, and consequences. Higher average exposure to MM advertising was associated with higher average use, intentions to use, positive expectancies, and negative consequences. Similarly, higher rates of change in MM advertising exposure were associated with higher rates of change in use, intentions, expectancies, and consequences over seven years. Results suggest that exposure to MM advertising may not only play a significant role in shaping attitudes about marijuana, but may also contribute to increased marijuana use and related negative consequences throughout adolescence. This highlights the importance of considering regulations for marijuana advertising, similar to regulations in place for the promotion of tobacco and alcohol in the U.S.

2018 Fairman et al discovered that more young people are choosing marijuana before cigarettes and alcohol. This is especially prevalent among young men of specific racial and ethnic groups in the US.Young people who start off on marijuana before alcohol or tobacco are more likely to become heavy users and have cannabis-related problems later in life.The research team analyzed nationally-representative, cross-sectional survey data available as part of the US National Survey on Drug Use and Health. This data draws on information from more than 275,500 individuals aged 12 to 21 and was collected between 2004 and 2014. Survey respondents were asked about their use of marijuana, cigarettes, alcohol, and other forms of tobacco or illegal drugs. Those who used these substances provided further information about which they started using first, and at what age.The researchers found that 8 per cent of participants reported in 2014 that marijuana was the first drug they ever used. This percentage had almost doubled from 4.8 per cent in 2004. According to Fairman, this could be related to a concurrent decline in those who start smoking cigarettes first, which dropped from about 21 per cent in 2004 to 9 per cent in 2014. They also observed a significant increase in youth abstaining from substance use altogether, which rose from 36 per cent to 46 per cent, and therefore, but said it is unclear the degree to which increases in those initiating marijuana first could be due to youth abstaining or delaying cigarettes. They also found that those using marijuana first, rather than alcohol or cigarettes, were more likely to be male, and Black, American Indian/Alaskan Native, multiracial, or Hispanic. The researchers established that youths who used marijuana first were more likely to become heavy users later in life, and to develop a cannabis use disorder.

2018 Hall et al said, 'It is premature to expand access to medicinal cannabis in hopes of solving the US Opioid crisis'. '*There is very weak evidence to support the claim that expanding access to medical cannabis will reduce opioid overdose deaths in the United States*'.

2018 Monitoring the Future study finds one in four of 12th graders admitting they would be more likely use marijuana if legalised. Overall, the rate of 12th graders saying they would not use marijuana if it were legalized fell 30% in the last ten years. Additionally, the rate of 12th graders who said they would use more marijuana if it were legal increased by almost 100% in the past decade. Interestingly, the survey also found that 17% of 12th graders today believe that their parents would not disapprove of marijuana use. This is almost double that of the 8% average from the late 1970s. the proportion of 12th graders who favour legalization of marijuana was at the highest level ever recorded, at 49%.

2018 Campbell et al investigated the effect of cannabis use in people with chronic non-cancer pain prescribed opioids –4 year prospective study. The Pain and Opioids IN Treatment study is a prospective, national, observational cohort of people with chronic non-cancer pain prescribed opioids. Participants were recruited through community pharmacies across Australia, completed baseline interviews, and were followed up with phone interviews or self-complete questionnaires yearly for 4 years. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were asked about lifetime and past year chronic pain conditions, duration of chronic non-cancer pain, pain self-efficacy, whether pain was neuropathic, lifetime and past 12-month cannabis use, number of days cannabis was used in the past month, and current depression and generalised anxiety disorder. We also estimated daily oral morphine equivalent doses of opioids. We used logistic regression to investigate cross-sectional associations with frequency of cannabis use, and lagged mixed-effects models to examine temporal associations between cannabis use and outcomes. Findings 1514 participants completed the baseline interview and were included in the study from Aug 20, 2012, to April 14, 2014. Cannabis use was common, and by 4-year follow-up, 295 (24%) participants had used cannabis for pain. Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years). At 4-year follow-up, compared with people with no cannabis use, we found that participants who used cannabis had a greater pain severity score (risk ratio 1·14, 95% CI 1·01–1·29, for less frequent cannabis use; and 1·17, 1·03–1·32, for daily or near-daily cannabis use), greater pain interference score (1·21, 1·09–1·35; and 1·14, 1·03–1·26), lower pain self-efficacy scores (0·97, 0·96–1·00; and 0·98, 0·96–1·00), and greater generalised anxiety disorder severity scores (1·07, 1·03–1·12; and 1·10, 1·06–1·15). We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation. Interpretation Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

2018 Christiansen and Bretteville-Jensen asked, 'Who seeks treatment for cannabis use? Abstract: There has been an absolute and relative increase in the number of patients with cannabis-related disorders as the principal diagnosis in many countries in recent years. Cannabis is now the most frequently mentioned problem drug reported by new patients in Europe, and cannabis patients constituted one third of all drug treatment patients in 2015. There is limited knowledge with regard to patient characteristics, the extent and types of health and psychosocial problems, as well as their association with long-term outcomes. Methods: We analysed indicators of physical, psychological and psychosocial problems of all patients admitted to treatment for cannabis use in Norway in 2009 and 2010 using register data and observed them to the end of 2013. Patient characteristics and outcomes were compared to a randomly drawn control group with corresponding age and gender distribution. Using logistic regression of prospective data, we studied associations between baseline characteristics and work and study status in 2013. Results: Cannabis patients tended to be relatively young and the large majority were male. They had parents who were less highly educated compared to controls, while there was no difference in migration background. In addition to an increased risk of premature death, nearly half of the patients received a secondary psychological diagnosis and a similar proportion received an additional substance use diagnosis during the 4–5 years of study follow-up. The cannabis patients were less educated than the control group and also less likely to be studying or working at the end of the study period. Entering treatment at a young age, having completed more than secondary education, having a highly-educated mother and not having a secondary diagnosis were factors that were positively associated with being in education or employment at the end of follow-up.

Conclusions: Data covering the entire Norwegian population of patients admitted primarily for cannabis-related problems showed comprehensive and complex patterns of physical, psychological and psychosocial problems. The prevalence and extent of these problems varied markedly from those of the general population. Work and study outcomes following treatment depended on the seriousness of the condition including co-morbidity as well as social capital.

2018 Heizer et al looked at marijuana misadventures in children. Abstract: A retrospective review was performed on children aged 31 days to 20 years who presented to Children's Hospital Colorado for care related to acute THC toxicity. The children were divided into groups based on exposure: group 1 (THC naïve) and group 2 (THC non-naïve). A total of 38 children (age, 3.5 [3] years) met inclusion for group 1 and an equal number of children (age, 15.1 [3.9] years) met the criteria for comparison in group 2. Eight naïve patients had documentation of estimated THC dose ingested (mean [SD], 7.13 [5.8] mg/kg; range, 2.9-19.5 mg/kg). A direct relationship between estimated oral THC dose, level of medical intervention required, and hospital disposition was observed. Lethargy/somnolence was more common in the naïve group (84% vs. 26%, $P < 0.0001$) whereas problems in cognition, perception, and behavior were more common in the non-naïve group (4% vs 11%, $P = 0.01$). The duration of clinical effect and length of hospital stay were longer in the naïve group (19.3 vs 5.0 hours, $P < 0.0001$) and (0.73 vs 0.19 days, $P < 0.0001$) respectively. There seems to be a direct relationship between the estimated oral THC dose (mg/kg), hospital disposition, and level of medical intervention required. Symptoms and duration of effects after THC exposure varied based on the route of exposure, age of patient, and history of previous THC experience.

2018 Rioux et al looked at the age of cannabis use and adult drug abuse symptoms. The present study examined 1) whether the associations between cannabis use (CU) age of onset and drug abuse by 28 y remain when controlling for risk factors in childhood, adolescence and early adulthood; and 2) the developmental pathways from early risk factors to drug abuse problems. Participants from a longitudinal sample of boys of low socioeconomic status (N = 1,030) were followed from 6 to 28 y. We examined the self-reported CU onset between the ages of 13 and 17 y and drug abuse symptoms by 28 y. The odds of developing any drug abuse symptoms by 28 y were reduced by 31% for each year of delayed CU onset (OR = 0.69). Cannabis, alcohol and other drug frequency at 17 y mediated this association. Still, even when taking that frequency of use into account, adolescents who started using cannabis before 15 y were at a higher risk of developing drug abuse symptoms by age 28 y. Significant indirect effects were found from early adolescent delinquency and affiliation with deviant friends to drug abuse symptoms at 28 y through CU age of onset and substance use frequency at 17 y. The results suggest more clearly than before that prevention programs should aim at delaying CU onset to prevent or reduce drug abuse in adulthood. Furthermore, prevention programs targeting delinquency and/or affiliation with deviant friends in childhood or early adolescence could indirectly reduce substance abuse in adulthood without addressing substance use specifically.

2018 Leos-Toro et al investigated perceived support fpor medical cannabis use among approved medical cannabis users in Canada. Abstract:Very little is known about the social experience of medical cannabis use, including the experience of stigma among approved users. The current study examined perceptions of support from physicians, family and friends as well as the prevalence of 'hiding' medicinal cannabis use.An online cross-sectional survey (N = 276) was conducted from 29 April to 8 June 2015. No public sampling frame was available from which to sample approved medical cannabis users (MCU). Eligible respondents were approved MCUs, aged 18 years or older, and reported cannabis use in the past 30 days for health reasons. Logistic regression analyses were used to assess aspects of stigma, including perceived support from their immediate social environment as well as behaviours reflecting a perceived social disapproval.Approximately one-third of respondents (32.6%) reported that their physician had refused to provide a medical document, and the vast majority of respondents (79.3%) reported hiding their medical cannabis use, most commonly to avoid judgement. Fewer than half of approved users perceived that their doctor was 'supportive' (38%), whereas two-thirds perceived support from family (66.3%) and friends (66.3%). Perceptions of support were similar across most socio-demographic sub-groups.Substantial proportions of approved MCUs in Canada report a lack of support and most have made some effort to conceal their medical cannabis use. Overall, the findings suggest that social norms around medical cannabis use remain unfavourable for many users, despite that fact that medical cannabis has been legal in Canada for more than a decade.

2018 Braun et al investigated medical oncologists' beliefs re medical marijuana. Abstract: Although almost every state medical marijuana (MM) law identifies cancer as a qualifying condition, little research supports MM's use in oncology. We hypothesized that the discrepancy between these laws and the

scientific evidence base poses clinical challenges for oncologists. Oncologists' beliefs, knowledge, and practices regarding MM were examined in this study. Methods In November 2016, we mailed a survey on MM to a nationally-representative, random sample of 400 medical oncologists. Main outcome measures included whether oncologists reported discussing MM with patients, recommended MM clinically in the past year, or felt sufficiently informed to make such recommendations. The survey also queried oncologists' views on MM's comparative effectiveness for several conditions (including its use as an adjunct to standard pain management strategies) and its risks compared with prescription opioids. Bivariate and multivariate analyses were performed using standard statistical techniques. Results The overall response rate was 63%. Whereas only 30% of oncologists felt sufficiently informed to make recommendations regarding MM, 80% conducted discussions about MM with patients, and 46% recommended MM clinically. Sixty-seven percent viewed it as a helpful adjunct to standard pain management strategies, and 65% thought MM is equally or more effective than standard treatments for anorexia and cachexia. Conclusion Our findings identify a concerning discrepancy between oncologists' self-reported knowledge base and their beliefs and practices regarding MM. Although 70% of oncologists do not feel equipped to make clinical recommendations regarding MM, the vast majority conduct discussions with patients about MM and nearly one-half do, in fact, recommend it clinically. A majority believes MM is useful for certain indications. These findings are clinically important and suggest critical gaps in research, medical education, and policy regarding MM.

2018 Karanges et al examined the knowledge and attitudes of Australian general practitioners (GP) towards medicinal cannabis, including patient demand, GP perceptions of therapeutic effects and potential harms, perceived knowledge and willingness to prescribe. A cross-sectional survey completed by 640 GPs (response rate=37%) attending multiple-topic educational seminars in five major Australian cities between August and November 2017. Number of patients enquiring about medicinal cannabis, perceived knowledge of GPs, conditions where GPs perceived it to be beneficial, willingness to prescribe, preferred models of access, perceived adverse effects and safety relative to other prescription drugs. The majority of GPs (61.5%) reported one or more patient enquiries about medicinal cannabis in the last three months. Most felt that their own knowledge was inadequate and only 28.8% felt comfortable discussing medicinal cannabis with patients. Over half (56.5%) supported availability on prescription, with the preferred access model involving trained GPs prescribing independently of specialists. Support for use of medicinal cannabis was condition-specific, with strong support for use in cancer pain, palliative care and epilepsy, and much lower support for use in depression and anxiety. The majority of GPs are supportive or neutral with regards to medicinal cannabis use. Our results highlight the need for improved training of GPs around medicinal cannabis, and the discrepancy between GP-preferred models of access and the current specialist-led models.

2018 Keyhani et al conducted a National Survey of US adults for their opinion of the risks and benefits of cannabis use. They used a probability-based online survey in the US 2017. 16,280 US adults were involved. They looked at the proportion of U.S. adults who agreed with a statement. The response rate was 55.3% (n = 9003). Approximately 14.6% of U.S. adults reported using marijuana in the past year. About 81% of U.S. adults believe marijuana has at least 1 benefit, whereas 17% believe it has no benefit. The most common benefit cited was pain management (66%), followed by treatment of diseases, such as epilepsy and multiple sclerosis (48%), and relief from anxiety, stress, and depression (47%). About 91% of U.S. adults believe marijuana has at least 1 risk, whereas 9% believe it has no risks. The most common risk identified by the public was legal problems (51.8%), followed by addiction (50%) and impaired memory (42%). Among U.S. adults, 29.2% agree that smoking marijuana prevents health problems. About 18% believe exposure to secondhand marijuana smoke is somewhat or completely safe for adults, whereas 7.6% indicated that it is somewhat or completely safe for children. Of the respondents, 7.3% agree that marijuana use is somewhat or completely safe during pregnancy. About 22.4% of U.S. adults believe that marijuana is not at all addictive. Wording of the questions may have affected interpretation. They concluded that Americans' view of marijuana use is more favorable than existing evidence supports.

2018 Moreno et al looked at marijuana promotions on social media and adolescents views on prevention strategies. Youth exposure to positive marijuana messages increases their risk of marijuana use. Since Washington State legalized recreational marijuana in 2012, marijuana businesses have used social media business pages to promote their products. Regulations to prevent youth access and targeting by marijuana businesses on social media in Washington State are absent. The purpose of this study was to engage youth in conceptualizing prevention approaches to limit youth exposure to marijuana business promotions on social media. Towards our goal of generating novel prevention approaches and promoting youth interaction to build ideas, we used focus groups. Adolescents ages 15-20 years in Washington State were recruited through purposeful sampling to achieve a diverse sample from six schools across two counties.

During focus groups, trained facilitators used a semi-structured guide to prompt discussion about marijuana business presence on social media. In the latter half of focus groups, facilitators showed example social media posts from marijuana businesses. All focus groups were audio recorded and manually transcribed. Qualitative analysis was conducted using the constant comparative method.A total of 32 adolescents with average age 17 years (SD = 0.6), 71% female, 43.8% Asian and 21.9% mixed race, participated in 5 focus groups. Recommendations for prevention focused in two main thematic areas. First, participants supported policies to restrict underage access to marijuana social media pages, an example quote was: "you have access to [the social media page] without being 21 and I think that's a problem." Second, participants proposed regulation of content that marijuana companies can post on social media, an example quote was: "I'm thinking they shouldn't be allowed to use children or anything associated with children and the memes that they post."Our findings indicate two strategies to limit youth exposure to marijuana content on social media. These specific strategies represent potential avenues to revise state policies and test the effectiveness of these approaches for states that permit recreational marijuana.

2018 Dupont et al looked at drug use among youth. National survey data support a common liability of all drug use. Abstract: The prevalence of substance use disorders in adults is higher if substance use is initiated during adolescence, underscoring the importance of youth substance use prevention. We examined whether the use of one substance by adolescents is associated with increased risk for using any other substance, regardless of use sequences. In 2017 we examined data from 17,000 youth aged 12-17 who participated in the 2014 National Survey on Drug Use and Health, a sample of nationally representative data on substance use among the U.S. civilian, noninstitutionalized population aged 12 or older. Descriptive analyses and multivariable logistic regression models were applied. After controlling for age, sex, and race/ethnicity, compared with youth without past-month marijuana use, youth with past-month marijuana use were 8.9 times more likely to report past-month cigarette use, 5.6, 7.9 and 15.8 times more likely to report past-month alcohol use, binge use, or heavy use (respectively), and 9.9 times more likely to report past-month use of other illicit drugs. The prevalence of past-month use of cigarettes, marijuana, and other illicit drugs was significantly higher among past-month alcohol users compared with youth without past-month alcohol use, and increased as intensity of alcohol use rose. Among past-month cigarette smokers, the prevalence of marijuana, other illicit drugs, and alcohol use were each significantly higher than youth without past-month cigarette use. Youth marijuana use, cigarette smoking, or alcohol consumption is associated with other substance use. This finding has importance for youth prevention, supporting a message no use by youth of any substance.

2018 Audrain-McGovern et al looked at adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. Abstract: Noncigarette tobacco products may confer a risk of marijuana use similar to combustible cigarettes. We examined whether adolescent electronic cigarette (e-cigarette), hookah, or combustible cigarette use is associated with initiating and currently using marijuana as well as using both tobacco and marijuana concurrently. Adolescents from 10 public schools in Los Angeles, California, completed in-classroom surveys at baseline (fall 2013, ninth grade) and at a 24-month follow-up (fall 2015, 11th grade). Among adolescents who never used marijuana at baseline (N = 2668), associations of baseline e-cigarette, hookah, or combustible cigarette use with ever marijuana use (initiation), current marijuana use (past 30 days), and current dual use of marijuana and these tobacco products at the 24-month follow-up were examined. Baseline ever versus never e-cigarette use was associated with initiation (odds ratio [OR] 3.63; 95% confidence interval [CI] 2.69‐4.90) and current (OR 3.67; 95% CI 2.51‐5.36) marijuana use 24 months later. Ever versus never hookah use was associated with initiation (OR 3.55; 95% CI 2.49‐5.08) and current (OR 4.10; 95% CI 2.69‐6.25) marijuana use 24 months later. Similar associations were observed for combustible cigarette smoking and initiation (OR 4.30; 95% CI 2.79‐6.63) and current use of marijuana (OR 1.97; 95% CI 1.05‐3.68). Current use of any of these tobacco products at baseline was associated with current use of both tobacco and marijuana (OR 2.28; 95% CI 1.47‐3.55) 24 months later. The association between tobacco use and subsequent marijuana use across adolescence extends to multiple tobacco products.

2018 Colizzi et al produced a longitudinal assessment of the effect of cannabis use on hospital re-admission rates in early psychosis. Abstract: Cannabis is the most commonly used illicit drug in psychosis patients and has been identified as a risk factor for relapse and subsequent hospital readmission, having substantial economic implications. To clarify the contribution of cannabis consumption to hospital readmission, a consecutive inpatient cohort of 161 early psychosis patients was included into the study. Data on cannabis use at admission and number of hospital readmissions and length of stay (LOS, number of inpatient days) in a 6-year follow-up was extracted from clinical notes. 62.4% of the patients had lifetime cannabis use. Their admission lasted on average 54.3 ± 75 days and over the following 6 years patients had 2.2 ± 2.8

hospital readmissions, for a total of 197.4 ± 331.5 days. Cannabis use significantly predicted the number of hospital readmissions and LOS in the following 6 years, the latter remaining significant after adjusting for use of other substance. Cannabis-using patients of male gender and Black ethnicity had a longer LOS at follow-up compared to female patients and other ethnic groups, respectively. Having a history of cannabis use when admitted to an early intervention inpatient unit for psychosis is associated with a higher number of subsequent hospital readmissions and a longer LOS, especially in male and Black patients.

2018 Stockings et al investigated cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions. 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.

2018 Marel et al looked at the progression from first use to use disorder on alcohol, cannabis, stimulants etc. Abstract: Relatively little is known about factors that may lead to the development of a substance use disorder (SUD), across a range of drug classes. This study aimed to identify factors that predict the likelihood of transition from use to SUD and the speed with which this may occur at the population level, with a focus on the impact of pre-existing mental disorders. Data were collected as part of the 2007 Australian National Survey of Mental Health and Wellbeing, a nationally representative survey of 8841 Australian adults. A series of discrete time survival analyses were undertaken on data pertaining to the age of onset of use and symptoms of use disorder, for alcohol, cannabis, sedatives, stimulants, and opioids, as well as the impact of pre-existing mood and anxiety disorders on the likelihood of developing a SUD. Lifetime cumulative probability estimates indicated that 50.4% of stimulant, 46.6% of opioid, 39% of sedative, 37.5% of alcohol, and 34.1% of cannabis users would develop a SUD on those substances, within an estimated 14, 12, 8, 30, and 23 years after onset respectively. Pre-existing mental disorders were significantly associated with increased risk of developing a SUD for alcohol, cannabis and stimulant use disorder. The relative speed associated with the transition from use to SUD emphasizes the narrow window of time available to intervene, underscoring the urgency of early identification of mental health conditions and the timely provision of appropriate evidence-based interventions, which could potentially prevent the development of secondary SUDs.

2018 Bleyer et al investigated the opioid death rate acceleration in jurisdictions legalising marijuana use. Two reports published in a recent issue of *JAMA Internal Medicine* describe 6% to 9% lower opioid prescribing rates for Medicare and Medicaid patients in states that legalized marijuana compared with states that have not. As cautioned in the accompanying editorial, however, “cannabis policy has raced ahead of cannabis science,” and more research is necessary to determine if marijuana availability ameliorates opioid mortality (marijuana-protection hypothesis).

2018 Akturk et al looked at an association between cannabis use and risk for diabetic ketoacidosis in adults with type 1 diabetes. Abstract:*While some evidence suggests that cannabis use may improve insulin sensitivity and pancreatic function in patients with type 1 diabetes, there also have been reports that it may be linked to diabetic ketoacidosis (DKA).* While some evidence suggests that cannabis use may improve insulin sensitivity and pancreatic function in patients with type 1 diabetes, there also have been reports that it may be linked to diabetic ketoacidosis (DKA). To investigate this possible association, researchers with the University of Colorado Anschutz Medical Campus and the Mayo Clinic queried 450 adults with type 1 diabetes about their demographic traits, diabetes history and complications, severe hypoglycemia requiring

assistance, and cannabis use. Nearly 30%, or 134 patients, said they had used cannabis. A relationship was observed between cannabis use during the prior year and elevated DKA risk compared with nonusers, which investigators suspect may be explained by the fact that cannabinoids alter gut motility and cause hyperemesis. Hemoglobin A1c levels also trended higher among cannabis users, but severe hypoglycemia was comparable between the two sets of patients. Because of the study's small scale, self-reported data, and other limitations, further research is needed to confirm the findings.

2018 Han et al looked at marijuana use by middle-age and older adults in the United States 2015-2016. Abstract: Marijuana use is increasing among middle-aged and older adults in the US, but little is understood of its pattern of use by this population. We performed a cross-sectional analysis of responses from 17,608 adults aged ≥50 years from the 2015 and 2016 administrations of the National Survey on Drug Use and Health. Prevalence of past-year marijuana use was estimated and compared between middle-aged adults (age 50–64) and older adults (≥65). Characteristics of past-year marijuana users including demographics, substance use, chronic disease, and emergency room use, were compared to non-marijuana users and stratified by age group. Marijuana use characteristics were also compared between middle-aged and older adults. We used multivariable logistic regression to determine correlates of past-year marijuana use. Prevalence of past-year marijuana use was 9.0% among adults aged 50–64 and 2.9% among adults aged ≥65. Prevalence of past-year alcohol use disorder (AUD), nicotine dependence, cocaine use, and misuse of prescription medications (i.e., opioids, sedatives, tranquilizers) were higher among marijuana users compared to non-users. In adjusted models, initiation of marijuana use <19 years of age [adjusted odds ratio (AOR) = 13.43, 95% confidence interval (CI) 9.60, 18.78)], AUD (AOR = 2.11, 95% CI 1.51, 2.94), prescription opioid misuse (AOR 2.49, 95% CI 1.61, 3.85), nicotine dependence (AOR = 1.90, 95% CI 1.59, 2.26), and cocaine use (AOR 7.43, 95% CI 4.23, 13.03), were all associated with increased odds of past-year marijuana use.Marijuana use is becoming more prevalent in this population and users are also at high risk for other drug use.

2018 Russo et al investigated low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) and found that they cause DNA damage and chromosomal aberrations in human-derived cells. Abstract: Cannabidiol (CBD) and cannabidivarin (CBDV) are natural cannabinoids which are consumed in increasing amounts worldwide in cannabis extracts, as they prevent epilepsy, anxiety, and seizures. It was claimed that they may be useful in cancer therapy and have anti-inflammatory properties. Adverse long-term effects of these drugs (induction of cancer and infertility) which are related to damage of the genetic material have not been investigated. Therefore, we studied their DNA-damaging properties in human-derived cell lines under conditions which reflect the exposure of consumers. Both compounds induced DNA damage in single cell gel electrophoresis (SCGE) experiments in a human liver cell line (HepG2) and in buccal-derived cells (TR146) at low levels (≥ 0.2 µM). Results of micronucleus (MN) cytome assays showed that the damage leads to formation of MNi which reflect chromosomal aberrations and leads to nuclear buds and bridges which are a consequence of gene amplifications and dicentric chromosomes. Additional experiments indicate that these effects are caused by oxidative base damage and that liver enzymes (S9) increase the genotoxic activity of both compounds. Our findings show that low concentrations of CBD and CBDV cause damage of the genetic material in human-derived cells. Furthermore, earlier studies showed that they cause chromosomal aberrations and MN in bone marrow of mice. Fixation of damage of the DNA in the form of chromosomal damage is generally considered to be essential in the multistep process of malignancy, therefore the currently available data are indicative for potential carcinogenic properties of the cannabinoids.

2018 Spindle et al compared the acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis. Abstract: Vaporization is an increasingly popular method for cannabis administration, and policy changes have increased adult access to cannabis drastically. Controlled examinations of cannabis vaporization among adults with infrequent current cannabis use patterns (>30 days since last use) are needed. The aim was to evaluate the acute dose effects of smoked This within-participant, double-blind, crossover study was conducted from June 2016 to January 2017 at the Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, and included 17 healthy adults. Six smoked and vaporized outpatient experimental sessions (1-week washout between sessions) were completed in clusters (order counterbalanced across participants); dose order was randomized within each cluster. Cannabis containing Δ 9-tetrahydrocannabinol (THC) doses of 0 mg, 10 mg, and 25 mg was vaporized and smoked by each participant. They looked for **c**hange from baseline scores for subjective drug effects, cognitive and psychomotor performance, vital signs, and blood THC concentration. Results The sample included 17 healthy adults (mean [SD] age, 27.3 [5.7] years; 9 men and 8 women) with no cannabis use in the prior month (mean [SD] days since last cannabis use, 398 [437] days). Inhalation of cannabis containing 10 mg of THC produced discriminative drug effects (mean [SD] ratings on a 100-point visual analog scale, smoked: 46 [26]; vaporized: 69 [26]) and

modest impairment of cognitive functioning. The 25-mg dose produced significant drug effects (mean [SD] ratings, smoked: 66 [29]; vaporized: 78 [24]), increased incidence of adverse effects, and pronounced impairment of cognitive and psychomotor ability (eg, significant decreased task performance compared with placebo in vaporized conditions). Vaporized cannabis resulted in qualitatively stronger drug effects for most pharmacodynamic outcomes and higher peak concentrations of THC in blood, compared with equal doses of smoked cannabis (25-mg dose: smoked, 10.2 ng/mL; vaporized, 14.4 ng/mL). Blood THC concentrations and heart rate peaked within 30 minutes after cannabis administration and returned to baseline within 3 to 4 hours. Several subjective drug effects and observed cognitive and psychomotor impairments persisted for up to 6 hours on average. They concluded that vaporized and smoked cannabis produced dose-orderly drug effects, which were stronger when vaporized. These data can inform regulatory and clinical decisions surrounding the use of cannabis among adults with little or no prior cannabis exposure.

2018 Tan et al investigated whether boys with social difficulties were more susceptible to early substance use. They concluded that boys who enter sixth-grade with co-occurring social skills, anxiety, learning and conduct problems are at the greatest risk of developing aggressive behavior and using tobacco, alcohol and marijuana by the end of eighth grade, a new study found.

2018 Wang et al investigated the impact of marijuana legalisation in Colorado on adolescent emergency and urgent care visits. Abstract: Approximately 6%-8% of U.S. adolescents are daily/past-month users of marijuana. However, survey data may not reliably reflect the impact of legalization on adolescents. The objective was to evaluate the impact of marijuana legalization on adolescent emergency department and urgent cares visits to a children's hospital in Colorado, a state that has allowed both medical and recreational marijuana. Retrospective review of marijuana-related visits by International Classification of Diseases codes and urine drug screens, from 2005 through 2015, for patients ≥ 13 and < 21 years old. From 2005 to 2015, 4,202 marijuana-related visits were identified. Behavioral health evaluation was obtained for 2,813 (67%); a psychiatric diagnosis was made for the majority (71%) of these visits. Coingestants were common; the most common was ethanol (12%). Marijuana-related visits increased from 1.8 per 1,000 visits in 2009 to 4.9 in 2015. (p = < .0001) Despite national survey data suggesting no appreciable difference in adolescent marijuana use, our data demonstrate a significant increase in adolescent marijuana-associated emergency department and urgent cares visits in Colorado.

2019 Keyes et al found that teens are increasingly choosing pot over alcohol, cigarettes etc.Abstract: In the past decade, marijuana use prevalence among adolescents has remained relatively steady while cigarette and alcohol prevalence has declined. We examined historical trends in: average grade of onset of marijuana, alcohol, and cigarette use by 12th grade; proportion who try alcohol/cigarettes before first marijuana use, among those who use by 12th grade; and conditional probability of marijuana use by 12th grade after trying alcohol/cigarettes. Data were drawn from 40 yearly, cross-sectional surveys of 12th grade US adolescents. A subset of students (N = 246,050) were asked when they first used each substance. We reconstructed cohorts of substance use from grade-of-onset to determine sequence of drug use, as well as probability of marijuana use in the same or later grade. Average grade of first alcohol and cigarette use by 12th grade increased across time; e.g., first cigarette increased from grade 7.9 in 1986 to 9.0 by 2016 (β=0.04, SE = 0.001, p < 0.01). The proportion of 12th grade adolescents who smoke cigarettes before marijuana fell below 50% in 2006. Each one-year increase was associated with 1.11 times increased odds of first cigarette in a grade after first marijuana (95% C.I. 1.11–1.12). Among those who initiate alcohol/cigarettes prior to marijuana by 12th grade, the probability of subsequent marijuana use is increasing. Marijuana is increasingly the first substance in the sequence of adolescent drug use. Reducing adolescent smoking has been a remarkable achievement of the past 20 years; those who continue to smoke are at higher risk for progression to marijuana use.

2019 Freeman et al looked at the increasing potency and price of cannabis in Europe 2006-2016. Abstract: Data was collected from 28 EU member states, Norway and Turkey by the European Monitoring Centre for Drugs and Drug Addiction. Outcome variables were potency, price, and value for cannabis resin and herbal cannabis in Europe, 2006-2016. Inflation was estimated using the Harmonised Indices of Consumer Prices. Mixed effects linear regression models were used to estimate linear and quadratic time trends, with a random intercept and slope fitted to account for variation across countries. Resin potency increased from a mean (95% CI) of 8.14% THC (6.89, 9.49) in 2006 to 17.22 (15.23, 19.25) in 2016. Resin price increased from 8.21 Euros/gram (7.54, 8.97) to 12.27 (10.62, 14.16). Resin increased in value, from 11.00 mg THC per Euro (8.60, 13.62) to 16.39 (13.68, 19.05). Quadratic time trends for resin potency and value indicated minimal change from 2006-2011, followed by marked increases from 2011-2016. Herbal cannabis potency increased from 5.00% THC (3.91, 6.23) to 10.22 (9.01, 11.47). Herbal price increased from 7.36 Euros/gram (6.22, 8.53) to 12.22 (10.59, 14.03). The value of herbal cannabis did not change from 12.65 mg of THC (10.18, 15.34) to 12.72 (10.73, 14.73). All price trends persisted after adjusting for inflation. European cannabis resin and herbal cannabis increased in potency and price from 2006-2016. Cannabis

resin (but not herbal cannabis) increased in the quantity of Δ9 -tetrahydrocannabinol per Euro spent. Marked increases in resin potency and value from 2011-2016 are consistent with the emergence of new resin production techniques in European and neighbouring drug markets'.

2019 CBD High Street CBD 'cannabis' oil to be banned for up to 18 months as experts probe whether it has any real health benefits Jan 30th 2019

The CDB oil is derived from cannabis but does not contain 'active' THC drug
The oil is promoted as a cure for anxiety, insomnia and joint and muscle pain
The Food Standards Agency says it counts as a 'novel food' and needs approval
So Trading Standards will be instructed to pull items from shops for 18 months

2019 Gauvin et al looked at marijuana toxicity due to heavy metal toxicity. Abstract: Federally unregulated, Marijuana Growth Organizations (MGOs) have now provided a path to exposures to the neurotoxicity of heavy metals. The lack of US Food and Drug Administration (FDA) and US Environmental Protection Agency (EPA) testing and oversight of the MGOs now threatens the public health. Agribusiness and botany experts proclaim the value of cannabis as a perfect rotating plant for phytoremediation programs to help scavenge heavy metals from soils prior to seeding the land for food product. Cannabis has a high affinity for soil contaminants without affecting its own heartiness. However, "legal" marijuana plots have burgeoned in the "Emerald Triangle" of Northern California, Oregon and Washington. According to the FDA's toxicology program, the largest sources of heavy metals (HMs) are the environments surrounding abandoned or active mines. The history of gold, platinum, coal, and copper mining in these grow areas now threatens the end-user; the plants ability to "scrub the earth" of these highly toxic HMs provides main stream smoke contamination to the consumer. Published reports of cannabis users showing hearing loss and neurological changes to temporal lobe structures involved in audition as well as learning and memory. The apoptotic cascade of cytotoxic events initiated by heavy metals is linked to the progression of Alzheimer's and Parkinson's disease, as well as hearing loss related to brain stem and temporal lobe neurotoxicity.

2019 Posis et al looked at indoor cannabis smoke and children's health. Abstract:Cannabis use is increasing and cannabis is typically consumed by smoking. This study explored how indoor secondhand cannabis smoke (SCS) was associated with child health. As part of a larger trial, air particle monitors were placed in 298 homes of families with at least one cigarette smoker and one child under 14 years old in San Diego County, California. Assessment included past 7-day indoor cigarette and cannabis use, the youngest child's exposure to cigarette smoke, and 5 smoke-related past-year child health outcomes: emergency department use for coughing/difficulty breathing; physician diagnosis of ear infection, bronchitis/bronchiolitis, asthma, or eczema/atopic dermatitis. An ordinal measure of adverse health outcomes (0, 1, or ≥2) was regressed on reported indoor cannabis smoking—the main measure of exposure (yes/no). Of 221 parents/guardians asked about cannabis use, 192 (86.9%) provided all required data, and 29 (15.1%) reported indoor cannabis smoking; reports were supported by air particle data. Homes without indoor smoking had lower average 7-day particle concentrations (1987 particles/0.01ft3) than homes with cannabis smoking only (3111 particles/0.01ft3), cigarette smoking only (3163 particles/0.01ft3), or both cigarette and cannabis smoking (5619 particles/0.01ft3). Odds of reporting a greater number of adverse health outcomes were 1.83 (95% CI = 0.89–3.80, $p = 0.10$) times higher for children of families with indoor cannabis smoking vs families without cannabis smoking, after controlling for exposure to cigarette smoke and other covariates. Our results do not indicate a statistically significant association. However, the magnitude of the (non-significant) association between indoor cannabis smoking and adverse health outcomes warrants more studies.

2018 Habboushe et al investigated the prevelance of cannabinoid hyperemesis syndrome among regular marijuana smokers in an urban public hospital. Abstract: Epidemiological data, including prevalence, for cannabinoid hyperemesis syndrome (CHS) remain largely unknown. Without these data, clinicians often describe CHS as 'rare' or 'very rare' without supporting evidence. We seek to estimate the prevalence of CHS in a population of patients presenting to a socio-economically and racially diverse urban Emergency Department of a public hospital. This study consisted of a questionnaire administered to a convenience sample of patients presenting to the ED of the oldest public hospital in the United States. Trained Research Associates (RAs) administered the questionnaire to patients between the ages of 18-49 years who reported smoking marijuana at least 20 days per month. The survey included questions related to CHS symptoms (nausea and vomiting) and Likert scale rankings on eleven symptom relief methods, including 'hot showers'. Patients were classified as experiencing a phenomenon consistent with CHS if they reported smoking marijuana at least 20 days per month and also rated 'hot showers' as five or more on the ten-point symptom relief method Likert scale for nausea and vomiting. Among 2127 patients approached for participation, 155 met inclusion criteria as smoking 20 or more days per month. Among those surveyed, 32.9% (95% CI, 25.5-40.3%) met our criteria for having experienced

CHS. If this is extractable to the general population, approximately 2.75 million (2.13-3.38 million) Americans may suffer annually from a phenomenon similar to CHS.

2018 Szaflarski et al investigated long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies. ABSTRACT:Since 2014, cannabidiol (CBD) has been administered to patients with treatment-resistant epilepsies (TREs) in an ongoing expanded-access program (EAP). We report interim results on the safety and efficacy of CBD in EAP patients treated through December 2016. METHODS:Twenty-five US-based EAP sites enrolling patients with TRE taking stable doses of antiepileptic drugs (AEDs) at baseline were included. During the 4-week baseline period, parents/caregivers kept diaries of all countable seizure types. Patients received oral CBD starting at 2-10 mg/kg/d, titrated to a maximum dose of 25-50 mg/kg/d. Patient visits were every 2-4 weeks through 16 weeks and every 2-12 weeks thereafter. Efficacy endpoints included the percentage change from baseline in median monthly convulsive and total seizure frequency, and percentage of patients with ≥50%, ≥75%, and 100% reductions in seizures vs baseline. Data were analyzed descriptively for the efficacy analysis set and using the last-observation-carried-forward method to account for missing data. Adverse events (AEs) were documented at each visit.RESULTS:Of 607 patients in the safety dataset, 146 (24%) withdrew; the most common reasons were lack of efficacy (89 [15%]) and AEs (32 [5%]). Mean age was 13 years (range, 0.4-62). Median number of concomitant AEDs was 3 (range, 0-10). Median CBD dose was 25 mg/kg/d; median treatment duration was 48 weeks. Add-on CBD reduced median monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks; reductions were similar through 96 weeks. Proportion of patients with ≥50%, ≥75%, and 100% reductions in convulsive seizures were 52%, 31%, and 11%, respectively, at 12 weeks, with similar rates through 96 weeks. CBD was generally well tolerated; most common AEs were diarrhea (29%) and somnolence (22%).SIGNIFICANCE:Results from this ongoing EAP support previous observational and clinical trial data showing that add-on CBD may be an efficacious long-term treatment option for TRE.

> 2018. Finn explains why marijuana will not fix the opioid epidemic. There is sufficient and expanding evidence demonstrating that medical marijuana use will not curb the opioid epidemic. There is further evidence that marijuana is a companion drug rather than substitution drug and that marijuana use may be contributing to the opioid epidemic rather than improving it. Although there are patients who have successfully weaned off of their opioids and use marijuana instead, the evidence that marijuana will replace opioids is simply not there. Medical provider and patient awareness, utilization of prescription drug monitoring programs, widespread availability and use of naloxone, and increasing coverage for atypical opioids and abuse deterrent formulations are only some of the other factors which hopefully be contributing to any impact on the opioid crisis. Education and prevention efforts as well as medication assisted therapies will be additional benefits to impact the opioid epidemic. Physicians should continue to monitor their patients closely, perform random drug testing to detect opioid misuse or aberrant behavior, and intervene early with alternative therapies when possible. Marijuana alone is certainly not the answer.

2018 Reece and Hulse investigated the Impacts of cannabinoid epigenetics on human development: reflections on Murphy et. al. 'cannabinoid exposure and altered DNA methylation in rat and human sperm' epigenetics 2018; 13: 1208-1221. Abstract: Recent data from the Kollins lab ('Cannabinoid exposure and altered DNA methylation in rat and human sperm' Epigenetics 2018; 13: 1208–1221) indicated epigenetic effects of cannabis use on sperm in man parallel those in rats and showed substantial shifts in both hypo- and hyper-DNA methylation with the latter predominating. This provides one likely mechanism for the transgenerational transmission of epigenomic instability with sperm as the vector. It therefore contributes important pathophysiological insights into the probable mechanisms underlying the epidemiology of prenatal cannabis exposure potentially explaining diverse features of cannabis-related teratology including effects on the neuraxis, cardiovasculature, immune stimulation, secondary genomic instability and carcinogenesis related to both adult and pediatric cancers. The potentially inheritable and therefore multigenerational nature of these defects needs to be carefully considered in the light of recent teratological and neurobehavioural trends in diverse jurisdictions such as the USA nationally, Hawaii, Colorado, Canada, France and Australia, particularly relating to mental retardation, age-related morbidity and oncogenesis including inheritable cancerogenesis. Increasing demonstrations that the epigenome can respond directly and in real time and retain memories of environmental exposures of many kinds implies that the genome-epigenome is much more sensitive to environmental toxicants than has been generally realized. Issues of long-term multigenerational inheritance amplify these concerns. Further research particularly on the epigenomic toxicology of many cannabinoids is also required

2019 Lewis et al looked at the engagement with medical cannabis information from online and mass media sources: is it related to medical cannabis attitudes and support for legaliation? Abstract:This study uses data

from an online survey of Israeli adults (N = 554) to test the association between information seeking and scanning about medical cannabis (from mass media and online sources) and attitudes toward medical cannabis. Furthermore, we test indirect effects of media engagement on attitudes toward cannabis legalization through medical cannabis attitudes. Seeking and scanning for information about medical cannabis from online sources, but not from mass media sources, were associated with positive attitudes toward medical cannabis. Engagement with medical cannabis information from online sources was also indirectly associated with greater support for cannabis legalization, through positive attitudes related to medical cannabis. The results suggest that one mechanism through which medical cannabis legalization is associated with cannabis legalization for all purposes is public engagement with information about medical cannabis in the media, particularly from the internet and social media channels. As increasingly more jurisdictions are expected to legalize medical cannabis, with resulting increase in media attention, support for recreational cannabis legalization may be expected to grow.

2019 Thomas et al looked at unintentional pediatric marijuana exposure prior to and after legalisation and commercial availability of recreational marijuana in Washington State. Abstract: Data were obtained from the WAPC database, toxiCALL®. Patients ≤ 9 years old with a reported marijuana exposure between July 2010 and July 2016 were included in the analysis. Patient and exposure characteristics were summarized and median exposure frequencies were calculated for the periods prior to and after legalization. There were 161 cases meeting the inclusion criteria that occurred between July 2010 and July 2016. Of these, 130 (81%) occurred in the 2.5-year period after legalization of recreational marijuana in January 2013. The median age of exposed children was 2 years (range 0–9 years). Eighty-one percent of the exposures occurred in the child's own home. The number of exposures per month increased after recreational marijuana was legalized in November 2012, and increased further once recreational marijuana shops were legally allowed to open in July 2014.Reported unintentional pediatric marijuana exposure has increased in the state of Washington since recreational marijuana was legalized. As marijuana becomes more available, clinicians should be aware of the risk of unintentional pediatric marijuana exposure, and this should inform lawmakers regarding regulations around childhood exposure to marijuana.

2019 Arterberry et al looked at higher average potency across the United Staea to find out if it is associated with progression to first cannabis use disorder symptom. Abstract: Data sources were the Michigan Longitudinal Study, an ongoing prospective, high-risk family study investigating the course and predictors for substance use disorders among youth beginning prior to school entry and time-parallel national average trends in delta-9-tetrahydrocannabinol (i.e., psychoactive compound in cannabis). The national average trends in delta-9-tetrahydrocannabinol were used to estimate potency level for the individual. Only cannabis users were included in analyses (n = 527). Cox regression showed an increased risk of progression from cannabis initiation to cannabis use disorder symptom onset by 1.41 times ($p < .001$) for each unit increase in national average delta-9-tetrahydrocannabinol as compared to those not endorsing CUD symptom onset, adjusting for sex, regular use, and cohort effects. Accounting for regular use, individuals initiating cannabis at national average 4.9% delta-9-tetrahydrocannabinol were at 1.88 times ($p = .012$) higher risk for cannabis use disorder symptom onset within one year compared to those who did not endorse CUD symptom onset, while those initiating cannabis at national average 12.3% delta-9-tetrahydrocannabinol were at 4.85 times ($p = .012$) higher risk within one year. This study provides prospective evidence suggesting higher potency cannabis, on average in the U.S., increases risk for onset of first cannabis use disorder symptom. Development of guidelines regarding cannabis potency is critical for reducing the costs associated with negative health outcomes.

2019 Donovan et al looked for a relationship between cannabis use and patient-supported symptoms in cancer patients seeking supportive palliative care. Abstract: We conducted a retrospective review of objectively measured tetrahydrocannabinol (THC) and subjectively reported cannabis use, its demographic and clinical correlates, and patient-reported symptoms in 816 cancer patients in active treatment referred to a supportive/palliative care outpatient clinic for specialized symptom management between January 2014 and May 2017. Nearly one-fifth (19.12%) tested positive for THC on urine drug testing. Users were younger, more likely to be men, single, and to have a history of cigarette smoking. Users also were likely to be more recently diagnosed and to have received radiotherapy. Certain moderate-to-severe symptoms, such as lack of appetite, shortness of breath, tiredness, difficulty sleeping, anxiety, and depression, were associated with use after accounting for sociodemographic and clinical differences between cannabis users and nonusers. Findings suggest patients seeking specialized symptom management are self-treating with cannabis, despite the lack of high-quality evidence for its use in palliative care. Unsanctioned use is likely to increase in cancer patients. Accurate information is urgently needed to help manage patient expectations for its use and increase understanding of risks and benefits.

2019 Reece et al explained the contemporary patterns of cannabis teratology. Cannabis has been shown to be teratogenic in cells, animals and humans. Particular targets of prenatal exposure include brain, heart and blood vessels and chromosomal segregation. Three longitudinal clinical studies report concerning cortical dysfunction persisting into adolescence and beyond, which are pertinent to the autism epidemic.Increased rates of congenital heart defects, gastroschisis, anencephaly and others have been reported. The pattern of neuroteratology seen after cannabis exposure strongly suggests a spectrum of dysfunction from mild to moderate to very severe. Downs syndrome, atrial septal defect (secundum type), ventricular septal defect and anotia / microtia were noted to be more common in prenatally cannabis exposed children in a large US epidemiological study which would appear to have been confirmed by recent experience in Colorado and other USA states. Studies in cells, together with the above mentioned epidemiology, implicate cannabidiol, cannabichromene, cannabidivarin and other cannabinoids in significant genotoxicity and / or epigenotoxicity. Notch signalling has recently been shown to be altered by cannabinoids, which is highly pertinent to morphogenesis of the neuraxis and cardiovasculature, and also to congenital and inheritable cancer induction. It is felt that subtle neurobehavioural psychosocial and educational deficits will likely be the most common expression of cannabinoid teratology at the population level. The far reaching implications of this wide spectrum of neuroteratological, pediatric cardiological and other defects and deficits should be carefully considered in increasingly liberal paradigms. Hence it is shown that the disparate presentations of cannabis teratology relate directly and closely to the distribution of CB1R's across the developing embryo and Cannabis has been shown to be teratogenic in cells, animals and humans. Particular targets of prenatal exposure include brain, heart and blood vessels and chromosomal segregation. Three longitudinal clinical studies report concerning cortical dysfunction persisting into adolescence and beyond, which are pertinent to the autism epidemic.Increased rates of congenital heart defects, gastroschisis, anencephaly and others have been reported. The pattern of neuroteratology seen after cannabis exposure strongly suggests a spectrum of dysfunction from mild to moderate to very severe. Downs syndrome, atrial septal defect (secundum type), ventricular septal defect and anotia / microtia were noted to be more common in prenatally cannabis exposed children in a large US epidemiological study which would appear to have been confirmed by recent experience in Colorado and other USA states. Studies in cells, together with the above mentioned epidemiology, implicate cannabidiol, cannabichromene, cannabidivarin and other cannabinoids in significant genotoxicity and / or epigenotoxicity. Notch signalling has recently been shown to be altered by cannabinoids, which is highly pertinent to morphogenesis of the neuraxis and cardiovasculature, and also to congenital and inheritable cancer induction. It is felt that subtle neurobehavioural psychosocial and educational deficits will likely be the most common expression of cannabinoid teratology at the population level. The far reaching implications of this wide spectrum of neuroteratological, pediatric cardiological and other defects and deficits should be carefully considered in increasingly liberal paradigms. Hence it is shown that the disparate presentations of cannabis teratology relate directly and closely to the distribution of CB1R's across the developing embryo and account for the polymorphous clinical presentations.

2019 Rogers et al investigated opioids and cannabis co-use among adults with chronic pain. Abstract: Opioid misuse constitutes a significant public health problem and is associated with a host of negative outcomes. Despite efforts to curb this increasing epidemic, opioids remain the most widely prescribed class of medications. Prescription opioids are often used to treat chronic pain despite the risks associated with use, and chronic pain remains an important factor in understanding this epidemic. Cannabis is another substance that has recently garnered attention in the chronic pain literature, as increasing numbers of individuals use cannabis to manage chronic pain. Importantly, the co-use of substances generally is associated with poorer outcomes than single substance use, yet little work has examined the impact of opioid-cannabis co-use. The current study examined the use of opioids alone, compared to use of opioid and cannabis co-use, among adults (n=450) with chronic pain on mental health, pain, and substance use outcomes. Results suggest that, compared to opioid use alone, opioid and cannabis co-use was associated with elevated anxiety and depression symptoms, as well as tobacco, alcohol, cocaine, and sedative use problems, but not pain experience. These findings highlight a vulnerable population of polysubstance users with chronic pain, and indicates the need for more comprehensive assessment and treatment of chronic pain.

2019 BMJ: Medicinal Use of Cannabis-based Products and Cannabinoids.What you need to know

- Cannabis based products for medicinal use contain cannabinoids derived from the cannabis plant, including Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of THC and CBD. Synthetic cannabinoids for medicinal use typically mimic the effects of specific cannabinoids such as THC

- THC is the constituent of cannabis that causes the "high," whereas CBD is not intoxicating at typical doses. THC and CBD have contrasting mechanisms of action and therapeutic indications; THC carries a higher risk of adverse events compared with CBD
- Rescheduling on 1 November 2018 permits some unlicensed cannabis based products to be prescribed for the first time in the UK, but only by doctors on the relevant Specialist Register of the General Medical Council
- Indications for treatment, supported by evidence of low to moderate certainty, include chronic pain, some treatment resistant epilepsies, and nausea and vomiting caused by chemotherapy
- Non-medicinal CBD products are legal and widely available on the internet and from health food retailers, but they lack quality standards and should not be used for medicinal purposes

2019 Monte et al looked at acute illness associated with cannabis use caused by route of exposure. Abstract: Little is known about the relative harms of edible and inhalable cannabis products. Objective was to describe and compare adult emergency department (ED) visits related to edible and inhaled cannabis exposure. Chart review of ED visits between 1 January 2012 and 31 December 2016. A large urban academic hospital in Colorado. Adults with ED visits with a cannabis-related International Classification of Diseases, Ninth or 10th Revision, Clinical Modification (ICD-9-CM or ICD-10-CM), code. Patient demographic characteristics, route of exposure, dose, symptoms, length of stay, disposition, discharge diagnoses, and attribution of visit to cannabis. Results:There were 9973 visits with an ICD-9-CM or ICD-10-CM code for cannabis use. Of these, 2567 (25.7%) visits were at least partially attributable to cannabis, and 238 of those (9.3%) were related to edible cannabis. Visits attributable to inhaled cannabis were more likely to be for cannabinoid hyperemesis syndrome (18.0% vs. 8.4%), and visits attributable to edible cannabis were more likely to be due to acute psychiatric symptoms (18.0% vs. 10.9%), intoxication (48% vs. 28%), and cardiovascular symptoms (8.0% vs. 3.1%). Edible products accounted for 10.7% of cannabis-attributable visits between 2014 and 2016 but represented only 0.32% of total cannabis sales in Colorado (in kilograms of tetrahydrocannabinol) in that period. Limitation: Retrospective study design, single academic center, self-reported exposure data, and limited availability of dose data. Conclsions:Visits attributable to inhaled cannabis are more frequent than those attributable to edible cannabis, although the latter is associated with more acute psychiatric visits and more ED visits than expected.

2019 Workforce Drug Testing Positivity Climbs to Highest Rate Since 2004, According to New Quest Diagnostics Analysis. The rate of workforce drug positivity hit a fourteen-year high in 2018 according to more than ten million workplace drug test results. Positivity rates in the combined U.S. workforce increased nearly 5% in urine drug tests, climbing to the highest level since 2004. The positivity rate is now more than 25% higher than the thirty-year low of 3.5% recorded between 2010 and 2012. Marijuana continues to top the list of the most commonly detected illicit substances, Marijuana positivity increased across nearly all employee testing categories

2019 Agrawal et al looked at alcohol, cigarette and cannabis use between 2002 and 2016 in pregnant women. In the National Survey of Drug Use and Health, the adjusted prevalence of past 30-day cannabis use in pregnant women aged 18 to 44 years rose from 2.37% in 2002 to 3.85% in 2014.[1] Another study found a relatively similar increase from 4.2% in 2009 to 7.1% in 2014.[2] Corresponding rates of alcohol use (eg, 11.2% from 2001-2005 vs 10.2% from 2011-2013) and cigarette smoking (eg, 13.3% in 2002 vs 12.3% in 2010) during pregnancy have generally decreased.[3-5] These reports encourage more detailed characterization of patterns of substance use during the course of pregnancy.

2019 Twardovski et al looked at the Effects of Cannabis Use on Sedation Requirements for Endoscopic Procedures.Abstract: Cannabis (or marijuana) became legal for recreational use in Colorado in 2012, and this legislation change has created both challenges and opportunities in medicine. More patients are using cannabis, and more patients are now willing to admit cannabis use than in the past, which increases the likelihood that they will be forthcoming about use during medical questioning. Cannabis use may have implications during medical care, including procedural sedation.OBJECTIVE:To determine whether regular cannabis use had any effect on the dose of medication needed for sedation during endoscopic procedures.METHODS:A total of 250 medical records were reviewed from 1 endoscopy center and 1 endoscopist to minimize the variability in sedation technique for the study purposes. The cohort was reviewed with regard to age and gender to determine whether differences were present among different groups as to the relative amount of sedation medication required in cannabis users vs nonusers. RESULTS: Medical records from 250 patients were reviewed, and researchers found that compared with people who did not regularly use cannabis, people who regularly used cannabis required an amount of sedation for endoscopic procedures that was significantly higher (P=.05). The statistical significance persisted when adjusted for age, sex, and use of alcohol, benzodiazepines, and opiates. CONCLUSION: Determining cannabis use before procedural sedation can be an important tool for planning patient care and assessing both medication needs and possible risks related to increased dosage

requirements during endoscopic procedures.

2019 Abuhasira et al investigated the epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. There is a substantial growth in the use of medical cannabis in recent years and with the aging of the population, medical cannabis is increasingly used by the elderly. We aimed to assess the characteristics of elderly people using medical cannabis and to evaluate the safety and efficacy of the treatment. A prospective study that included all patients above 65 years of age who received medical cannabis from January 2015 to October 2017 in a specialized medical cannabis clinic and were willing to answer the initial questionnaire. Outcomes were pain intensity, quality of life and adverse events at six months. During the study period, 2736 patients above 65 years of age began cannabis treatment and answered the initial questionnaire. The mean age was 4.5 ± 7.5 years. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). After six months of treatment, 93.7% of the respondents reported improvement in their condition and the reported pain level was reduced from a median of 8 on a scale of 0-10 to a median of 4. Most common adverse events were: dizziness (9.7%) and dry mouth (7.1%). After six months, 18.1% stopped using opioid analgesics or reduced their dose. CONCLUSION: Our study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative

2019 Seltenrich investigated pesticide regulating in cannabis. Abstract: Outside Sonoma Lab Works' otherwise ordinary building in an anonymous business park, the distinct odor of pot pervades the air. However, it's not just any pot. It is the smell of strictly regulated, professionally cultivated, rigorously tested legal cannabis. Past the heavily tinted front door, the airy 8,000-square-foot facility is filled with fluorescent light and the hum of machines. Anyone who has ever visited a university chemistry department will recognize the long, white coats. Located on the outskirts of Santa Rosa, California, Sonoma Lab Works is one of 49 independent third-party laboratories statewide tasked with ensuring that the state's legal weed is also clean. It is not a simple task. For a price of $890 per sample,Sonoma Lab Works will run a full panel of tests on any cannabis-based product, in accordance with strict new state regulations rolled out over the course of 2018.Using instruments costing hundreds of thousands of dollars each, trained technicians take high-precision measurements of potency, moisture content, residual solvents, heavy metals, mycotoxins, microbial impurities, and pesticides.Products that do not meet the state's standards cannot be sold—legally, anyway.These rules represent the best efforts of California's recently formed Bureau of Cannabis Control (BCC) to protect consumers in the state's multibillion-dollar market. However, people within the burgeoning industry and the environmental health field have widely differing views of how well the BCC regulations accomplish that goal, particularly regarding pesticides. At least one thing is clear: California's response to the challenge has implications well beyond state lines.

2019 Tucker et al looked at types of cannabis and tobacco/nicotine co-usee and associated outcomes in young adulthood. Abstract: Cannabis and tobacco/nicotine use are highly comorbid. Given expanding access to cannabis through legalization for recreational use, it is important to understand how patterns of cannabis and tobacco/nicotine co-use are associated with young adult outcomes. A predominantly California-based sample of 2,429 young adults (mean age = 20.7) completed an online survey. Based on past-year reports of cannabis and tobacco/nicotine use, we defined 5 mutually exclusive groups: (a) single-product use; (b) concurrent use only (using both products, but only on separate occasions); (c) sequential use only (using both products on the same occasion, one right after the other, but not mixing them together); (d) coadministration only (using both products on the same occasion by mixing them in the same delivery device); and (e) both sequential use and coadministration. We examined group differences in use patterns, dependence, consequences of use, and psychosocial functioning. Fifty percent of respondents reported cannabis use, 43% tobacco/nicotine use, and 37% co-use of both substances. The most prevalent method of co-use involved smoking combustible products. Overall, individuals who co-used both substances on the same occasion in some way reported heavier use and greater problematic behaviors than those who did not. Sequential use (especially among those that also engaged in coadministration) was typically associated with worse physical and mental functioning overall compared to using each substance separately. Findings illuminate both prevalence and risks associated with co-use of cannabis and tobacco/nicotine products and can inform policies for states considering regulation of cannabis and tobacco/nicotine products.

2019 Arkell et al found that CBD content in vaporized cannabis does not prevent THC-induced impairment of driving and cognition. Abstrat: The present study investigated and compared the effects of THC-dominant and THC/CBD equivalent cannabis on simulated driving and cognitive performance. In a randomized, double-blind, within-subjects crossover design, healthy volunteers ($n = 14$) with a history of light cannabis use attended three outpatient experimental test sessions in which simulated driving and cognitive performance were assessed at two timepoints (20–60 min and 200–240 min) following vaporization of 125 mg THC-dominant (11% THC; < 1% CBD), THC/CBD equivalent (11% THC, 11% CBD), or placebo (< 1% THC/CBD) cannabis. Both active cannabis types increased lane weaving during a car-following task but had little effect on other driving performance measures. Active cannabis types impaired performance on the Digit Symbol Substitution Task (DSST), Divided Attention Task (DAT) and Paced Auditory Serial Addition Task (PASAT) with impairment on the latter two tasks worse with THC/CBD equivalent cannabis. Subjective drug effects (e.g., "stoned") and confidence in driving ability did not vary with CBD content. Peak plasma THC concentrations were higher following THC/CBD equivalent cannabis relative to THC-dominant cannabis, suggesting a possible pharmacokinetic interaction. Cannabis containing equivalent concentrations of CBD and THC appears no less impairing than THC-dominant cannabis, and in some circumstances, CBD may actually exacerbate THC-induced impairment.

2019 Reece et al looked at the effect of cannabis legalization on US autism Incidence and medium term projections. Objective: In that cannabis use has been linked with the development of autism spectrum disorder like conditions in gestationally exposed children, we set out to explore the extent to which rising cannabis use might contribute to the rising autism epidemic. Methods: Datasets from US Department of Education Individuals with Disabilities Act (IDEA), National Survey of Drug Use and Health, and CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network were investigated. Data on legal status was derived from SAMHSA. Results: IDEA had N=1,023 and ADDM N=87. Modelling of IDEA consistently showed that models quadratic-intime out-performed linear-only models. In both datasets, liberalisation of cannabis legislationwas associated with increased ASD. Slopes of ASD v time, cannabis v time and ASD v cannabis curves cannabis curves were shown to be related on graphical analysis by geofacet plots and tanglegrams (entanglement=0.3326). CDC's ADDM network quoted US autism incidence 168/10,000 in 2014. IDEA projections indicated rates 108.57, 131.67 and 166.49 in cannabis-illegal, -medical and -decriminalized states rising exponentially to 282.37, 396.91 and 455.54 by 2030. Conclusion: ASD is the commonest form of cannabis-associated clinical teratology. Using two independent datasets and two categorization methods we confirmed that medical, decriminalized and legal cannabis regimes are associated with higher rates of ASD than illegal ones. Findings are consistent with molecular, cellular and epigenetic mechanisms. Formerly quadratic regression curves become exponential when projected forwards to 2030; predict a lower quantum than the 2014 ADDM CDC figure; and indicate a 60% excess of cases in legal states by 2030.

2019 Ewing et al looked into the hepatoxicity of a cannabidiol-rich cannabis extract in the mouse model. The goal of this study was to investigate Cannabidiol (CBD) hepatotoxicity in 8-week-old male B6C3F1 mice. Animals were gavaged with either 0, 246, 738, or 2460 mg/kg of CBD (acute toxicity, 24 h) or with daily doses of 0, 61.5, 184.5, or 615 mg/kg for 10 days (sub-acute toxicity). These doses were the allometrically scaled mouse equivalent doses (MED) of the maximum recommended human maintenance dose of CBD in EPIDIOLEX® (20 mg/kg). In the acute study, significant increases in liver-to-body weight (LBW) ratios, plasma ALT, AST, and total bilirubin were observed for the 2460 mg/kg dose. In the sub-acute study, 75% of mice gavaged with 615 mg/kg developed a moribund condition between days three and four. As in the acute phase, 615 mg/kg CBD increased LBW ratios, ALT, AST, and total bilirubin. Hepatotoxicity gene expression arrays revealed that CBD differentially regulated more than 50 genes, many of which were linked to oxidative stress responses, lipid metabolism pathways and drug metabolizing enzymes. In conclusion, CBD exhibited clear signs of hepatotoxicity, possibly of a cholestatic nature. The involvement of numerous pathways associated with lipid and xenobiotic metabolism raises serious concerns about potential drug interactions as well as the safety of CBD.

2019 Mason et al conducted a systematic review of research on solitary alcohol and marijuana use in the United States. BACKGROUND AND AIMS:Alcohol use and marijuana use tend to be social activities among adolescents. Some youth use alcohol or marijuana while alone. This article provides a framework for examining the risk factors for and consequences of solitary alcohol and marijuana use, grounded in a motivational model that emphasizes coping with negative emotions, and provides the first systematic review of research on solitary alcohol and marijuana use among middle school- and high school-aged

adolescents in the United States.METHODS:PubMed, PsycINFO and Web of Science were searched. Articles were included if they mention solitary alcohol or marijuana (or illicit drug) use among adolescents aged 12-18 years. Studies on non-human animals, college students, non-English language publications and articles exclusively about solitary tobacco or inhalant use were excluded. Overall, 22 articles were selected.RESULTS:Prevalence of adolescent solitary alcohol and marijuana use was relatively high (e.g. 14% life-time solitary drinking in the general adolescent population), particularly in high-risk subgroups (e.g. 38.8% life-time solitary drinking in a sample of youth recruited from clinical and community settings). Risk factors for solitary alcohol and marijuana use include earlier onset and heavier use, coping motives, negative emotions and positive expectancies about use. Solitary alcohol and marijuana use are prospectively associated with later substance use disorder (SUD) symptoms, diminished academic performance and perceived health.CONCLUSIONS:Approximately 1 in 7 adolescents in the US appear to have engaged in solitary alcohol and marijuana use at some point. It is positively associated with extent of drinking and marijuana use, cop;ing motives, negative emotions, and positive expectancies, as well as subsequent SUD symptoms and poor academic and health-related outcomes.

2019Young-Wolff et al Looked at self-reported daily, weekly and monthly cannabis use among women before and during pregnancy Abstract:. Cross-sectional study using data from 367 403 pregnancies among 276 991 women 11 years or older who completed a self-administered questionnaire on cannabis use during standard prenatal care in Kaiser Permanente Northern California from January 1, 2009, to December 31, 2017. The annual prevalence of self-reported daily, weekly, and monthly cannabis use among women before and during pregnancy was estimated using Poisson regression with a log link function, adjusting for sociodemographics. Data analyses were conducted from February to May 2019. EXPOSURES: Calendar year. MAIN OUTCOMES AND MEASURES: Self-reported frequency of cannabis use in the year before pregnancy and during pregnancy assessed as part of standard prenatal care (at approximately 8 weeks' gestation). RESULTS: Among the overall sample of 367 403 pregnancies among 276 991 women, 35.9% of the women self-reported white race/ethnicity; 28.0%, Hispanic; 16.6%, Asian; 6.0%, African American; and 13.5%, other. In the sample, 1.2% of the women were aged 11 to 17 years; 15.3%, 18 to 24 years; 61.4%, 25 to 34 years; and 22.0%, older than 34 years. Median (interquartile range) neighborhood household income was $70 472 ($51 583-$92 643). From 2009 to 2017, the adjusted prevalence of cannabis use in the year before pregnancy increased from 6.80% (95% CI, 6.42%-7.18%) to 12.50% (95% CI, 12.01%-12.99%), and the adjusted prevalence of cannabis use during pregnancy increased from 1.95% (95% CI, 1.78%-2.13%) to 3.38% (95% CI, 3.15%-3.60%). Annual relative rates of change in self-reported daily cannabis use (1.115; 95% CI, 1.103-1.128), weekly cannabis use (1.083; 95% CI, 1.071-1.095), and monthly or less cannabis use (1.050; 95% CI, 1.043-1.057) in the year before pregnancy increased significantly, with daily use increasing most rapidly (from 1.17% to 3.05%). Similarly, annual relative rates of change in self-reported daily cannabis use (1.110; 95% CI, 1.089-1.132), weekly cannabis use (1.075; 95% CI, 1.059-1.092) and monthly or less cannabis use (1.044; 95% CI, 1.032-1.057) during pregnancy increased significantly from 2009 to 2017, with daily use increasing most rapidly (from 0.28% to 0.69%). Results of this study demonstrate that frequency of cannabis use in the year before pregnancy and during pregnancy has increased in recent years among pregnant women in Northern California, potentially associated with increasing acceptance of cannabis use and decreasing perceptions of cannabis-associated harms.

2019 Hazekamp looked at the trouble with CBD Oil. Abstract: In just a few years, cannabidiol (CBD) has become immensely popular around the world. After initially being discovered as an effective self-medication for Dravet syndrome in children, CBD is now sold and used to treat a wide range of medical conditions and lifestyle diseases. The cannabinoid CBD, a non-psychoactive isomer of the more infamous tetrahydrocannabinol (THC), is available in a growing number of administration modes, but the most commonly known is CBD oil. There are currently dozens, if not hundreds, of producers and sellers of CBD oils active in the market, and their number is increasing rapidly. Those involved vary from individuals who prepare oils on a small scale for family and (Facebook) friends to compounding pharmacies, pharmaceutical companies, and licensed cannabis producers. Despite the growing availability of CBD, many uncertainties remain about the legality, quality, and safety of this new “miracle cure.” As a result, CBD is under scrutiny on many levels, ranging from national health organizations and agricultural lobbyists to the WHO and FDA. The central question is whether CBD is simply a food supplement, an investigational new medicine, or even a narcotic. This overview paper looks into the known risks and issues related to the composition of CBD products, and makes recommendations for better regulatory control based on accurate labeling and more scientifically supported health claims. The intention of this paper is to create a better understanding of the benefits versus the risks of the current way CBD products are produced, used, and advertised.

2019 Miller et al examined the regulation of Intraocular pressure. Abstract: It has been known for nearly 50 years that cannabis and the psychoactive constituent Δ9-tetrahydrocannabinol (THC) reduce intraocular pressure (IOP). Elevated IOP remains the chief hallmark and therapeutic target for glaucoma, a major cause of blindness. THC likely acts via one of the known cannabinoid-related receptors (CB1, CB2, GPR18, GPR119, GPR55) but this has never been determined explicitly. Cannabidiol (CBD) is a second major constituent of cannabis that has been found to be without effect on IOP in most studies.: Effects of topically applied THC and CBD were tested in living mice by using tonometry and measurements of mRNA levels. In addition the lipidomic consequences of CBD treatment were tested by using lipid analysis.We now report that a single topical application of THC lowered IOP substantially (∼28%) for 8 hours in male mice. This effect is due to combined activation of CB1 and GPR18 receptors each of which has been shown to lower ocular pressure when activated. We also found that the effect was sex-dependent, being stronger in male mice, and that mRNA levels of CB1 and GPR18 were higher in males. Far from inactive, CBD was found to have two opposing effects on ocular pressure, one of which involved antagonism of tonic signaling. CBD prevents THC from lowering ocular pressure. We conclude that THC lowers IOP by activating two receptors—CB1and GPR18—but in a sex-dependent manner. CBD, contrary to expectation, has two opposing effects on IOP and can interfere with the effects of THC.

2019 Whitehill et al looked at the incidence of pediatric cannabis exposure among children and teenagers from 0 to 19 before and after medical marijuana legalisation in Massachusettes. Cross-sectional comparison of pediatric cannabis exposure cases 4 years before and after MML in Massachusetts. The exposure cases included those of 218 children and teenagers aged between 0 and 19 years, as reported to the RPC from 2009 to 2016. Census data were used to determine the incidence. Data analysis was performed from November 12, 2018, to July 20, 2019. MAIN OUTCOMES AND MEASURES: Incidence of RPC-reported cannabis exposure cases, both single substance and polysubstance, for the age group of 0 to 19 years, and cannabis product type, coingestants, and clinical effects. RESULTS: During the 8-year study period (2009-2016), the RPC received 218 calls involving cannabis exposure (98 single substance, 120 polysubstance) in children and teenagers aged 0 to 19 years, representing 0.15% of all RPC calls in that age group for that period. Of the total exposure cases, males accounted for 132 (60.6%) and females 86 (39.4%). The incidence of single-substance cannabis calls increased from 0.4 per 100 000 population before MML to 1.1 per 100 000 population after (incidence rate ratio, 2.4; 95% CI, 1.5-3.9), a 140% increase. The age group of 15 to 19 years had the highest frequency of RPC-reported cannabis exposures (178 calls [81.7%]). The proportion of all RPC calls due to single-substance cannabis exposure increased overall for all age groups from 29 before MML to 69 afterward. Exposure to edible products increased after MML for most age groups. CONCLUSIONS AND RELEVANCE:Pediatric cannabis exposure cases increased in Massachusetts after medical marijuana was legalized in 2012, despite using childproof packaging and warning labels. This study provides additional evidence suggesting that MML may be associated with an increase in cannabis exposure cases among very young children, and extends prior work showing that teenagers are also experiencing increased cannabis-related health system contacts via the RPC. Additional efforts are needed to keep higher-potency edible products and concentrated extracts from children and teenagers, especially considering the MML and retail cannabis sales in an increasing number of US states.

2019 Demontis et al looked at CHRNA2 in cannabis use disorder. Abstract:
Cannabis is the most frequently used illicit psychoactive substance worldwide; around one in ten users become dependent. The risk for cannabis use disorder (CUD) has a strong genetic component, with twin heritability estimates ranging from 51 to 70%. Here we performed a genome-wide association study of CUD in 2,387 cases and 48,985 controls, followed by replication in 5,501 cases and 301,041 controls. We report a genome-wide significant risk locus for CUD ($P = 9.31 \times 10\text{-}12$) that replicates in an independent population ($P_{replication} = 3.27 \times 10\text{-}3$, $P_{meta\text{-}analysis} = 9.09 \times 10\text{-}12$). The index variant (rs56372821) is a strong expression quantitative trait locus for cholinergic receptor nicotinic α2 subunit (CHRNA2); analyses of the genetically regulated gene expression identified a significant association of CHRNA2 expression with CUD in brain tissue. At the polygenic level, analyses revealed a significant decrease in the risk of CUD with increased load of variants associated with cognitive performance. The results provide biological insights and inform on the genetic architecture of CUD.

2019 Roberts looked at legalised cannabis in Colorado emergency departments. Abstract: Cannabis legalization has led to significant health consequences, particularly to patients in emergency departments and hospitals in Colorado. The most concerning include psychosis, suicide, and other substance abuse. Deleterious effects on the brain include decrements in complex decision-making, which may not be reversible with abstinence. Increases in fatal motor vehicle collisions, adverse effects on cardiovascular and pulmonary systems, inadvertent pediatric exposures, cannabis contaminants exposing users to infectious agents, heavy metals, and pesticides, and hash-oil burn injuries in preparation of drug concentrates have been documented. Cannabis

dispensary workers ("budtenders") without medical training are giving medical advice that may be harmful to patients. Cannabis research may offer novel treatment of seizures, spasticity from multiple sclerosis, nausea and vomiting from chemotherapy, chronic pain, improvements in cardiovascular outcomes, and sleep disorders. Progress has been slow due to absent standards for chemical composition of cannabis products and limitations on research imposed by federal classification of cannabis as illegal. Given these factors and the Colorado experience, other states should carefully evaluate whether and how to decriminalize or legalize non-medical cannabis use.

2019 Linden-Carmichael et al investigated whether marijuana may boost the risky effects of alcohol.Summary: Compared to people who only drank alcohol, those who used alcohol and marijuana simultaneously were more likely to drink heavier and more often, according to researchers. They were also more likely to experience alcohol-related problems -- like impulsive actions they later regretted.

2019 Chadi et al looked at the association between electronic cigarette use and marijuana use among adolescents and young adults. Abstract: PubMed, Embase, and Web of Science & ProQuest Dissertations and Theses were searched from inception to October 2018. A gray-literature search was also conducted on conference abstracts, government reports, and other sources. STUDY SELECTION: Included studies compared rates of marijuana use among youth aged 10 to 24 years who had used e-cigarettes vs those who had not used e-cigarettes. Two reviewers independently assessed studies for inclusion; disagreements were discussed with a third reviewer and resolved by consensus.DATA EXTRACTION AND SYNTHESIS:Data were extracted by 2 independent reviewers following Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines and pooled using a random-effects analysis. The Newcastle-Ottawa Scale was used to assess data quality and validity of individual studies.MAIN OUTCOMES AND MEASURES:Adjusted odds ratios (AORs) of self-reported past or current marijuana use by youth with vs without past or current e-cigarette use.RESULTS:Twenty-one of 835 initially identified studies (2.5%) met selection criteria. The meta-analysis included 3 longitudinal and 18 cross-sectional studies that included 128 227 participants. Odds of marijuana use were higher in youth who had an e-cigarette use history vs those who did not (AOR, 3.47 [95% CI, 2.63-4.59]; I2, 94%). Odds of marijuana use were significantly increased in youth who used e-cigarettes in both longitudinal studies (3 studies; AOR, 2.43 [95% CI, 1.51-3.90]; I2, 74%) and cross-sectional studies (18 studies; AOR, 3.70 [95% CI, 2.76-4.96]; I2, 94%). Odds of using marijuana in youth with e-cigarette use were higher in adolescents aged 12 to 17 years (AOR, 4.29 [95% CI, 3.14-5.87]; I2, 94%) than young adults aged 18 to 24 years (AOR, 2.30 [95% CI, 1.40-3.79]; I2, 91%). CONCLUSIONS AND RELEVANCE: This meta-analysis found a significant increase in the odds of past or current and subsequent marijuana use in adolescents and young adults who used e-cigarettes. These findings highlight the importance of addressing the rapid increases in e-cigarette use among youths as a means to help limit marijuana use in this population.

2019 Meir et al looked at cannabis concentrate use in adolescents. **Abstract:** Cannabis concentrates, which are cannabis plant extracts that contain high concentrations of Δ-9-tetrahydrocannbinol (THC), have become increasingly popular among adults in the United States. However, no studies have reported on the prevalence or correlates of cannabis concentrate use in adolescents, who, as a group, are thought to be particularly vulnerable to the harms of THC.
METHODS: Participants are a racially and ethnically diverse group of 47 142 8th-, 10th-, and 12th-grade students recruited from 245 schools across Arizona in 2018. Participants reported on their lifetime and past-month marijuana and cannabis concentrate use, other substance use, and risk and protective factors for substance use problems spanning multiple life domains (ie, individual, peer, family, school, and community).
RESULTS: Thirty-three percent of all 8th-, 10th-, and 12th-graders reported lifetime cannabis use, and 24% reported lifetime concentrate use. Seventy-two percent of all lifetime cannabis users had used concentrates. Relative to adolescent cannabis users who had not used concentrates, adolescent concentrate users were more likely to use other substances and to experience more risk factors, and fewer protective factors, for substance use problems across numerous life domains.
CONCLUSIONS: Most adolescent cannabis users have used concentrates. Based on their risk and protective factor profile, adolescent concentrate users are at higher risk for substance use problems than adolescent cannabis users who do not use concentrates. Findings raise concerns about high-risk adolescents exposure to high-THC cannabis.

2019 Rotermenn analysed the trends in the prevalence of cannabis use and related metrics in Canada. Data from the Canadian Tobacco, Alcohol and Drugs Survey and the Canadian Tobacco Use Monitoring Survey were used to examine longer-term (historical) rates of use during 2004 to 2017. Five iterations of the National Cannabis Surveys (NCS) (2018-2019) were used to examine current use (overall, daily or almost daily (DAD), quantities, and types of products) in the months before and after legalization. RESULTS:From 2004 through 2017 cannabis use decreased among 15 to 17 year olds, remained stable for 18 to 24 year olds, and increased among adults aged 25 to 64. During 2018 and into 2019, rates of cannabis use increased overall from 14% to 18%; with statistically significant increases also for males generally (16% to 22%) and males aged 18 to 64. Rates of cannabis use remained largely stable for females (13%) and seniors (4%). In 2019, about 60% of consumers reported using one cannabis product; use of dried cannabis (flower/leaf) was the most common (84.2%). The average user

consumed 27.5 grams of dried cannabis (flower/leaf) over three months; amounts consumed varied depending on use frequency (e.g. occasional users: 2.6 grams/3 months versus DAD users: 62.6 grams/3 months). DISCUSSION:Results highlight the importance of understanding pre-legalization behaviours as changes in use after legalization may have begun prior to the legislation. NCS allows for the early impacts of legalisation to be examined and provides a picture of not only changes in who is using but also what and how much.

2019 Gardiner et al reported that health professionals were wary of medicinal cannabis use and its adverse effects. 26 published studies conducted in Australia, the United States, Canada, Ireland and internationally were analysed These studies assessed the beliefs, knowledge and concerns about medicinal cannabis held by medical practitioners, nurses, pharmacists and allied health professionals Generally, health professionals supported clinical use of medicinal cannabis, however they said they lacked knowledge across all aspects, from pharmacology and dosing to legislation around access, distribution and supply Their greatest concerns about the drug were patient harm, adverse drug interactions and whether cannabis would be obtained 'medicinally' as a legal guise for recreational use

2019 Shover et al found that the Association between medical cannabis laws and opioid overdose mortality has reversed over time. Medical cannabis has been touted as a solution to the US opioid overdose crisis since Bachhuber et al. [M. A. Bachhuber, B. Saloner, C. O. Cunningham, C. L. Barry, *JAMA Intern. Med.* 174, 1668–1673] found that from 1999 to 2010 states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality. That research received substantial attention in the scientific literature and popular press and served as a talking point for the cannabis industry and its advocates, despite caveats from the authors and others to exercise caution when using ecological correlations to draw causal, individual-level conclusions. In this study, we used the same methods to extend Bachhuber et al.'s analysis through 2017. Not only did findings from the original analysis not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from −21% to +23% and remained positive after accounting for recreational cannabis laws. We also uncovered no evidence that either broader (recreational) or more restrictive (low-tetrahydrocannabinol) cannabis laws were associated with changes in opioid overdose mortality. We find it unlikely that medical cannabis—used by about 2.5% of the US population—has exerted large conflicting effects on opioid overdose mortality. A more plausible interpretation is that this association is spurious. Moreover, if such relationships do exist, they cannot be rigorously discerned with aggregate data. Research into therapeutic potential of cannabis should continue, but the claim that enacting medical cannabis laws will reduce opioid overdose death should be met with skepticism.

2019 Freeman et al reported on the medical use of Cannabis-based producta and cannabinoids: What you need to know:

- Cannabis based products for medicinal use contain cannabinoids derived from the cannabis plant, including Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of THC and CBD. Synthetic cannabinoids for medicinal use typically mimic the effects of specific cannabinoids such as THC
- THC is the constituent of cannabis that causes the "high," whereas CBD is not intoxicating at typical doses. THC and CBD have contrasting mechanisms of action and therapeutic indications; THC carries a higher risk of adverse events compared with CBD
- Rescheduling on 1 November 2018 permits some unlicensed cannabis based products to be prescribed for the first time in the UK, but only by doctors on the relevant Specialist Register of the General Medical Council
- Indications for treatment, supported by evidence of low to moderate certainty, include chronic pain, some treatment resistant epilepsies, and nausea and vomiting caused by chemotherapy)
- Non-medicinal CBD products are legal and widely available on the internet and from health food retailers, but they lack quality standards and should not be used for medicinal purposes

2019 Layden et al investigated pulmonary illness related to e-cigarette use in Illinois and Wisconsin. Abstract:E-cigarettes are battery-operated devices that heat a liquid and deliver an aerosolized product to the user. Pulmonary illnesses related to e-cigarette use have been reported, but no large series has been described. In July 2019, the Wisconsin Department of Health Services and the Illinois Department of Public Health received reports of pulmonary disease associated with the use of e-cigarettes (also called vaping) and launched a coordinated public health investigation. We defined case patients as persons who reported use of e-cigarette devices and related products in the 90 days before symptom onset and had

pulmonary infiltrates on imaging and whose illnesses were not attributed to other causes. Medical record abstraction and case patient interviews were conducted with the use of standardized tools. There were 53 case patients, 83% of whom were male; the median age of the patients was 19 years. The majority of patients presented with respiratory symptoms (98%), gastrointestinal symptoms (81%), and constitutional symptoms (100%). All case patients had bilateral infiltrates on chest imaging (which was part of the case definition). A total of 94% of the patients were hospitalized, 32% underwent intubation and mechanical ventilation, and one death was reported. A total of 84% of the patients reported having used tetrahydrocannabinol products in e-cigarette devices, although a wide variety of products and devices was reported. Syndromic surveillance data from Illinois showed that the mean monthly rate of visits related to severe respiratory illness in June through August of 2019 was twice the rate that was observed in the same months in 2018. Case patients presented with similar clinical characteristics. Although the features of e-cigarette use that were responsible for injury have not been identified, this cluster of illnesses represents an emerging clinical syndrome or syndromes. Additional work is needed to characterize the pathophysiology and to identify the definitive causes.

2019 Blayer & Barnes looked st the contribution of marijuana legalisation to the US opioid Mortality Epidemic (not yet peer-reviewed). . **Abstract: Background:** Prior studies of U.S. states as of 2013 and one state as of 2015 suggested that marijuana availability reduces opioid mortality (marijuana protection hypothesis). This investigation tested the hypothesis with opioid mortality trends updated to 2017 and by evaluating all states and the District of Columbia (D.C.). **Methods:** Opioid mortality data obtained from the U.S. Centers for Disease Control and Prevention were used to compare opioid death rate trends in each marijuana-legalizing state and D.C. before and after medicinal and recreational legalization implementation and their individual and cumulative aggregate trends with concomitant trends in non-legalizing states. The Joinpoint Regression Program identified statistically-significant mortality trends and when they occurred. **Results:** Of 23 individually evaluable legalizing jurisdictions, 78% had evidence for a statistically-significant acceleration of opioid death rates after medicinal or recreational legalization implementation at greater rates than their pre-legalization rate or the concurrent composite rate in non-legalizing states. All four jurisdictions evaluable for recreational legalization had evidence ($p < 0.05$) for subsequent opioid death rate increases, one had a distinct acceleration, and one a reversal of prior decline. Since 2009-2012, when the cumulative-aggregate opioid death rate in the legalizing jurisdictions was the same as in the non-legalizing group, the legalizing group′s rate accelerated increasingly faster ($p=0.009$). By 2017 it was 67% greater than in the non-legalizing group ($p<0.05$). **Conclusions:** The marijuana protection hypothesis is not supported by recent U.S. data on opioid mortality trends. Instead, legalizing marijuana appears to have contributed to the nation′s opioid mortality epidemic.

2019 Fernandez et al discovered how marijuana use can increase your risk for an alcohol overdose. Abstract: Alcohol can lead to fatal and nonfatal overdose (OD) through its neurobiological inhibitory effects when used alone or with other drugs. Little research has examined alcohol OD characteristics in the context of concomitant drug use. This study utilized alcohol OD data (defined as alcohol poisoning, passing out, or blacking out) collected in a large residential addiction treatment facility ($N = 660$). Latent class analysis identified classes of alcohol OD events based on concomitant drug use at the time of OD. We evaluated correlates of alcohol OD classes, including depression, emergency medical services, and hospitalization, using latent class regression. Only 20% of alcohol ODs involved alcohol alone. Marijuana was the most commonly used drug during the most recent alcohol OD (43.2%), followed by sedatives (27.9%), cocaine or crack (25.9%), prescription opioids (26.1%), and heroin (20%). The final latent class model included 3 classes: no/low drug involvement (61%), moderate drug involvement (33%), and high drug involvement (6%). Relative to the no/low drug involvement class, participants admitted to the hospital were 6.4-fold more likely to be in the high drug involvement class (95% CI: 2.4 to 16.6) and 2.9-fold more likely to be in the moderate drug involvement class (95% CI: 1.2 to 7.2). Participants receiving emergency medical services were more likely to be in the high drug involvement class (aOR: 2.2, 95% CI: 2.2, 1.1 to 4.5) and less likely to be in the moderate drug involvement class (aOR 0.39, 95% CI: 0.2 to 0.96). Combining drug classes with alcohol prior to OD was common and associated with a higher likelihood of hospitalization. Overdose prevention efforts should address acute risks of alcohol ingestion with other drugs.

2019 Cerda et al investigated the association between recreational marijuana legalisation in the US and changes in marijuana use and CUD from 2008 to 2016. Problematic use of marijuana among adolescents and adults increased after legalization of recreational marijuana use, according to a new study from NYU Grossman School of Medicine and Columbia University Mailman School of Public Health.Published online November 13 in *JAMA Psychiatry*, the study is the first to look at the impact of recreational marijuana legalization on both use and cannabis use disorder (commonly referred to as problematic marijuana use)

across multiple age groups. Presently, 11 states and Washington, D.C. have legalized marijuana for recreational use while 33 states and D.C. have legalized marijuana for medical use.

2019 Madras et al looked at the associations of parental marijuanba use with offspring marijuana, alcohol and tobacco and opioid misuses. Abstract: Marijuana use is increasing among adults and often co-occurs with other substance use; therefore, it is important to examine whether parental marijuana use is associated with elevated risk of substance use among offspring living in the same household. To examine associations of parental marijuana use with offspring marijuana, tobacco, and alcohol use and opioid misuse. This cross-sectional study used survey data from the 2015 through 2018 National Surveys on Drug Use and Health (NSDUH), which provide nationally representative data on adolescents or young adults living with a parent (the mother or the father). Annual average percentages were based on survey sampling weights. Final analyses were conducted September 21 through 23, 2019. Parental marijuana use status. Offspring self-reported use of marijuana, tobacco, or alcohol or misuse of opioids. **Results** Survey respondents included 24 900 father-offspring or mother-offspring dyads sampled from the same household. Among mothers living with adolescent offspring, 8.2% (95% CI, 7.3%-9.2%) had past-year marijuana use, while 7.6% (95% CI, 6.2%-9.2%) of mothers living with young adult offspring had past-year marijuana use. Among fathers living with adolescent offspring, 9.6% (95% CI, 8.5%-10.8%) had past-year marijuana use, and 9.0% (95% CI, 7.4%-10.9%) of fathers living with young adult offspring had past-year marijuana use. Compared with adolescents whose mothers never used marijuana, adjusted relative risk (ARR) of past-year marijuana use was higher among those whose mothers had lifetime (without past-year) marijuana use (ARR, 1.3; 95% CI, 1.1-1.6; *P* = .007), less than 52 days of past-year marijuana use (ARR, 1.7; 95% CI, 1.1-2.7; *P* = .02), or 52 days or more of past-year marijuana use (ARR, 1.5; 95% CI, 1.1-2.2; *P* = .02). Compared with young adults whose mothers never used marijuana, adjusted risk of past-year marijuana use was higher among those whose mothers had lifetime (without past-year) marijuana use (ARR, 1.4; 95% CI, 1.1-1.7; *P* = .001), less than 52 days of past-year marijuana use (ARR, 1.5; 95% CI, 1.0-2.3; *P* = .049), or 52 days or more of past-year marijuana use (ARR, 1.8; 95% CI, 1.3-2.5; *P* = .002). Compared with adolescents whose fathers never used marijuana, adolescents whose fathers had less than 52 days of past-year marijuana use were more likely to use marijuana (ARR, 1.8; 95% CI, 1.2-2.7; *P* = .006). Compared with young adults whose fathers never used marijuana, young adults whose fathers had 52 days or more of past-year marijuana use were more likely to use marijuana (ARR, 2.1; 95% CI, 1.6-2.9; *P* < .001). Compared with their peers whose parents never used marijuana and after adjusting for covariates, the adjusted risk of past-year tobacco use was higher among adolescents whose mothers had lifetime marijuana use (ARR, 1.3; 95% CI, 1.0-1.6; *P* = .03), less than 52 days of past-year marijuana use (ARR, 1.5; 95% CI, 1.0-2.1; *P* = .04), or 52 days or more of past-year marijuana use (ARR, 1.6; 95% CI, 1.1-2.3; *P* = .03); adolescents whose fathers had lifetime marijuana use (ARR, 1.5; 95% CI, 1.1-1.9; *P* = .004) or 52 days or more of past-year marijuana use (ARR, 1.8; 95% CI, 1.2-2.7; *P* = .006); young adults whose mothers had lifetime marijuana use (ARR, 1.2; 95% CI, 1.0-1.4; *P* = .04); and young adults whose fathers had 52 days or more of past-year marijuana use (ARR, 1.4; 95% CI, 1.0-1.9; *P* = .046). Compared with their peers whose parents had no past marijuana use and after adjusting for covariates, risk of past-year alcohol use was higher among adolescents whose mothers had lifetime marijuana use (ARR, 1.2; 95% CI, 1.1-1.4; *P* = .004), less than 52 days of past-year marijuana use (ARR, 1.5; 95% CI, 1.2-1.9; *P* = .002), or 52 days or more of past-year marijuana use (ARR, 1.3; 95% CI, 1.0-1.7; *P* = .04). After adjusting for covariates, parental marijuana use was not associated with opioid misuse by offspring. **Conclusions and Relevance** In this cross-sectional study, parental marijuana use was associated with increased risk of substance use among adolescent and young adult offspring living in the same household. Screening household members for substance use and counseling parents on risks posed by current and past marijuana use are warranted.

2019 Steigerwaldt et al looked at differences in opinionabout marijuana use and prevalence of use by state legaliszation status: Abstract
Beliefs about marijuana use and prevalence of use may be associated with the legalization status of the state of residence. We examined differences in views and rates of use of marijuana among residents in recreationally legal, medically legal, and nonlegal states. We surveyed a nationally representative online panel of US adults (N = 16,280) and stratified results by marijuana legalization status of states. We compared views of residents of recreational states on benefits and risks of marijuana use to residents in other states.
The response rate was 56.3% (n = 9003). Residents in recreationally legal states were more likely to believe marijuana could be beneficial for pain management (73% in recreationally legal states, 67% in medically legal states, 63% in nonlegal states; *P* value: <0.0001), provide relief from stress, anxiety or depression (52% in recreationally legal states, 47% in medically legal states, 46% in nonlegal states; *P* value: 0.01), and improve appetite (39% in recreationally legal states, 36% in medically legal states, 33% in nonlegal states; *P* value: <0.009). In addition, residents in recreational states were

significantly more likely to believe that smoking 1 marijuana joint a day is somewhat or much safer than smoking 1 cigarette a day (40.8% in recreationally legal states, 39.1% in medically legal states, and 36.1% in nonlegal states; *P* value: <0.0001). Residents of recreationally and medically legal states were more likely to believe second-hand marijuana smoke was somewhat or much safer than second-hand tobacco smoke (38.3% in recreationally legal states, 38.3% in medically legal states, and 35.7% in nonlegal states; *P* value: 0.003). Past-year marijuana use in any form (20% in recreational, 14.1% in medical, 12% in nonlegal) and past-year marijuana use of multiple forms (11.1% in recreational, 6.1% in medical, 4.9% in nonlegal) were highest among residents of recreationally legal states. Overall, prevalence of past-year use of any form of marijuana use was more common among residents of recreationally legal states compared with other states (20.3%, confidence interval [CI] 19.5, 21.1 in recreationally legal states; 15.4%, CI 14.7, 16.2 in medically legal states; 11.9%, CI 11.2, 12.6 in nonlegal states).
Residents in recreationally legal states were most likely to believe marijuana has benefits, marijuana smoke is safer than tobacco smoke, and have the highest rate of marijuana use. This is cause for concern, given the tide of commercialization, growing number of high-potency cannabis products, and favorable media coverage promoting use for health problems. Residents in recreationally legal states were most likely to believe marijuana has benefits, marijuana smoke is safer than tobacco smoke, and have the highest rate of marijuana use. This is cause for concern, given the tide of commercialization, growing number of high-potency cannabis products, and favorable media coverage promoting use for health problems.

2019 Cuttler et al looked at short and long-term effects of cannabis on headache and migraine. Abstract: Use of cannabis to alleviate headache and migraine is relatively common, yet research on its effectiveness remains sparse. We sought to determine whether inhalation of cannabis decreases headache and migraine ratings as well as whether gender, type of cannabis (concentrate vs. flower), THC, CBD, or dose contribute to changes in these ratings. Finally, we explored evidence for tolerance to these effects. Archival data were obtained from StrainprintTM, a medical cannabis app that allows patients to track symptoms before and after using different strains and doses of cannabis. Latent change score models and multilevel models were used to analyze data from 12,293 sessions where cannabis was used to treat headache and 7,441 sessions where cannabis was used to treat migraine. There were significant reductions in headache and migraine ratings after cannabis use. Men reported larger reductions in headache than women and use of concentrates was associated with larger reductions in headache than flower. Further, there was evidence of tolerance to these effects. Perspective: Inhaled cannabis reduces self-reported headache and migraine severity by approximately 50%. However, its effectiveness appears to diminish across time and patients appear to use larger doses across time, suggesting tolerance to these effects may develop with continued use.

2019 Reece and Hulse looked at how cannabis consumption patterns explain the east-west gradient in Canadian neural tube defect incidence. While a known link between prenatal cannabis exposure and anencephaly exists, the relationship of prenatal cannabis exposure with neural tube defects (NTDs) generally has not been defined. Published data from Canada Health and Statistics Canada were used to assess this relationship. Both cannabis use and NTDs were shown to follow an east-west and north-south gradient. Last year cannabis consumption was significantly associated ($P < .0001$; cannabis use–time interaction $P < .0001$). These results were confirmed when estimates of termination for anomaly were used. Canada Health population data allowed the calculation of an NTD odds ratio) of 1.27 (95% confidence interval = 1.19-1.37; $P < 10^{-11}$) for high-risk provinces versus the remainder with an attributable fraction in exposed populations of 16.52% (95% confidence interval = 12.22-20.62). Data show a robust positive statistical association between cannabis consumption as both a qualitative and quantitative variable and NTDs on a background of declining NTD incidence. In the context of multiple mechanistic pathways these strong statistical findings implicate causal mechanisms.

2019 Reece and Hulse found that Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends. 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.

2019 Chandra et al looked at nw trends in cannabis potency in USA and Europe during the last decade 2008-2017. Through the potency monitoring program at the University of Mississippi supported by National Institute on Drug Abuse (NIDA), a total of 18108 samples of cannabis preparations have been analyzed over the last decade, using a validated GC/FID method. The samples are classified as sinsemilla,

marijuana, ditchweed, hashish, and hash oil (now referred to as cannabis concentrate). The number of samples received over the last 5 years has decreased dramatically due to the legalization of marijuana either for medical or for recreational purposes in many US states. The results showed that the mean Δ9-THC concentration has increased dramatically over the last 10 years, from 8.9% in 2008 to 17.1% in 2017. The mean Δ9-THC:CBD ratio also rose substantially from 23 in 2008 to 104 in 2017. There was also marked increase in the proportion of hash oil samples (concentrates) seized (0.5-4.7%) and their mean Δ9-THC concentration (6.7-55.7%) from 2008 to 2017. Other potency monitoring programs are also present in several European countries such as The Netherlands, United Kingdom, France, and Italy. These programs have also documented increases in Δ9-THC concentrations and Δ9-THC:CBD ratios in cannabis. These trends in the last decade suggest that cannabis is becoming an increasingly harmful product in the USA and Europe.

2020 Bao et al looked at a neonate death due to marijuana toxicity to the liver and adrenals.
BACKGROUND Marijuana is the considered the most widely available and used drug across the world. Up to this time, there have been no reports of human death directly caused by acute marijuana toxicity in adults, fetuses, or newborn neonates. CASE REPORT We report a death of an 11-day-old white female neonate due to acute marijuana toxicity. She died of extensive necrosis and hemorrhage of the liver and adrenals due to maternal use of marijuana. CONCLUSIONS This case is unique in that other possible causes of death can be eliminated. With growing use of marijuana by pregnant women and increases in newborn drug screening of umbilical cord homogenate, more cases of neonatal death due to acute marijuana toxicity could be discovered.

2020 Goodman et al looked at the prevalence and forms of cannabis use in legal vs. illegal redreational cannabis markets. Recreational or 'non-medical cannabis' has been legalized in several US states, and was legalized federally in Canada in October 2018. There is little comparative data on product use across jurisdictions, particularly with respect to the types of cannabis products used, which differentially impact health. Data are from Wave 1 of the International Cannabis Policy Study, collected from Aug 27–Oct 7, 2018. Respondents (n = 27,024) aged 16–65 completed an online survey measuring patterns of cannabis use, quantities and routes of administration. Respondents were recruited from Canada (n = 9976) and US states that had (n = 7362) and had not (n = 9686) legalized non-medical cannabis ('legal' and 'illegal' states, respectively).
Prevalence of at least daily, weekly, and monthly cannabis use were significantly higher in US 'legal' states (11.3%, 18.2%, 25.0%, respectively) than US 'illegal' states (7.4%, 11.6%, 16.8%, respectively; p<0.001) and Canada (8.9%, 14.1%, 19.0%, respectively; $p \leq 0.01$). Dried herb was the dominant form of cannabis reported by past 12-month users across all jurisdictions (77.7%–80.8%). Although the amount of dried herb used per year did not differ by jurisdiction (range: 210.3–229.4 g), those in US 'legal' states were significantly more likely to use dried herb daily or weekly than were those in 'illegal' states and Canada (p<0.001). Use of cannabis concentrates, vaped oils, edibles, and drinks was more prevalent among US 'legal' states than 'illegal' states and Canada ($p \leq 0.001$). Vaping dried herb was more common in both legal and illegal US jurisdictions than in Canada (p<0.05), whereas Canadians were more likely to smoke dried herb with tobacco (p<0.001).
The prevalence of cannabis use—and use of products such as cannabis concentrates, edibles and drinks—was higher in US states that had legalized cannabis. Additional longitudinal research is required to determine whether these differences reflect causal effects of legalization or pre-existing secular trends.

2020 Kruger et al looked at cannabis enthusiasts' knowledge of medical treatment effectiveness and increased risks of cannabis use.PURPOSE:To compare cannabis enthusiasts' knowledge about cannabis risks and effectiveness in treating medical conditions with existing empirical evidence. DESIGN:A brief survey assessed cannabis use, information sources, and knowledge about risks and effectiveness.SETTING:A cannabis advocacy event in April 2019 in a state with legal medical and recreational cannabis.PARTICIPANTS:Demographically diverse adults (N = 472) who frequently used cannabis; 85% used cannabis for health or medical purposes.MEASURES:Participants reported the sources of their cannabis information, health conditions they thought cannabis was effective in treating (n = 10), and health risks increased by cannabis (n = 6). Conditions and risks were based on ratings of evidence (ie, from substantial to insufficient) for therapeutic effects and risks identified in a review by The National Academies of Sciences, Engineering, and Medicine (NASEM, 2017).ANALYSES:Chi-square tests examined the correspondence between participants' knowledge and NASEM conclusions. RESULTS:Most participants' (95% confidence interval [CI]: 74%-81%) knowledge of cannabis was from their own experiences; 18% (95% CI: 14%-21%) received information from primary care providers. On average, participants' beliefs matched NASEM conclusions for half of effectiveness (95% CI: 50%-53%) and risk items (95% CI: 55%-57%). Many (95% CI: 38%-42%) thought that cannabis use did not increase any risk.

Contrary to NASEM conclusions, many thought cannabis was effective in treating cancer (76%), depressive symptoms (72%), and epilepsy (68%). Those who received cannabis information from their primary care providers had better knowledge of medical effectiveness. Medicinal cannabis use frequency inversely predicted knowledge of medical effectiveness and increased risks of adverse events.CONCLUSION:There were considerable discrepancies between cannabis users' knowledge and available evidence, highlighting the need for more research and education (by physicians, caregivers, and dispensaries) on effectiveness and health risks, especially for users with specific health issues such as pregnant women and people with depression.

2020 Block et al examined adolescent substance use through opportunity theory. ABSTRACTThe present study examines substance use behaviors of middle and high school students, focusing on how varying influences of opportunity measures impact use of specific types of substances. The data used in the present study come from almost 4,000 students within 89 school contexts from students attending public school in a Southern state. Hierarchical logistic modeling is used to explore the influence of various opportunities at both the student and school levels on the use of different types of substances. Results indicate measures of opportunity at both the student and school levels were significant; however, measures at the individual level were consistently more influential.

2020 Murray et al asked the question:'Will legalization and commercialization of cannabis use increase the incidence and prevalence of psychosis? He concluded:

Is it inevitable that legalization of recreational cannabis will result in more dependence and psychosis? In theory, it is possible to legalize cannabis in ways that do not increase potency and prevalence of use but, so far, experience with commercialization in North Americais not encouraging.Governmentsthat decide to legalizecannabis should usesomeof the tax revenue to monitor cannabis price, consumption, and potency levels and to carefully evaluate the longterm repercussions for mental health in different US states and Canadian provinces. Such monitoring would enable policies to be developed to minimize harm. In the absence of such an approach, itseemslikely that the current commercialization of recreational cannabis in North America will be followed in a fewyears by a rise in the incidence ofnewcases of psychosis and in the prevalence of people with more chronic psychoses.

2020 Reece et Hulse looked at Canadian cannabis consumption and patterns of congenital anomalies.Abstract: Cannabis is a known teratogen. Data availability addressing both major congenital anomalies and cannabis use allowed us to explore their geospatial relationships. Data for the years 1998 to 2009 from Canada Health and Statistics Canada was analyzed in R. Maps have been drawn and odds ratios, principal component analysis, correlation matrices, least squares regression and geospatial regression analyses have been conducted using the R packages base, dplyr, epiR, psych, ggplot2, colorplaner and the spml and spreml functions from package splm. Mapping showed cannabis use was more common in the northern Territories of Canada in the Second National Survey of Cannabis Use 2018. Total congenital anomalies, all cardiovascular defects, orofacial clefts, Downs syndrome and gastroschisis were all found to be more common in these same regions and rose as a function of cannabis exposure. When Canada was dichotomized into high and low cannabis use zones by Provinces v Territories the Territories had a higher rate of total congenital anomalies 450.026 v 390.413 (O.R. = 1.16 95%C.I. 1.08-1.25, $P = 0.000058$; attributable fraction in exposed 13.25%, 95%C.I. 7.04–19.04%). In geospatial analysis in a spreml spatial error model cannabis was significant both alone as a main effect ($P < 2.0 \times 10^{-16}$) and in all its first and second order interactions with both tobacco and opioids from $P < 2.0 \times 10^{-16}$. These results show that the northern Territories of Canada share a higher rate of cannabis use together with elevated rates of total congenital anomalies, all cardiovascular defects, Down's syndrome and gastroschisis. This is the second report of a significant association between cannabis use and both total defects and all cardiovascular anomalies and the fourth published report of a link with Downs syndrome and thereby direct major genotoxicity. The correlative relationships described in this paper are confounded by many features of social disadvantage in Canada's northern territories. However, in the context of a similar broad spectrum of defects described both in animals and in epidemiological reports from Hawaii, Colorado, USA and Australia they are cause for particular concern and indicate further research.

2020 Prashad et al investigated sex-related differences in subjective but not neural, cue-elicitated craving response in heavy cannabis users. Studies indicate that female cannabis users progress through the milestones of cannabis use disorder (CUD) more quickly than male users, likely due to greater subjective craving response in women relative to men. While studies have reported sex-related differences in subjective craving, differences in neural response and the relative contributions of neural and behavioral response remain unclear. We examined sex-related differences in neural and behavioral response to cannabis cues and cannabis use measures in 112 heavy cannabis users (54 females). We used principal component analysis to determine the relative contributions of neural and behavioral response and cannabis use measures.Results We found that principal component (PC) 1, which accounts for the most variance in the dataset, was correlated with neural response to cannabis cues with no differences between male and female users ($p = 0.21$). PC2, which accounts for the second-most variance, was correlated with subjective craving such that female users exhibited greater subjective craving relative to male users ($p = 0.003$). We also found that CUD symptoms correlated with both PC1 and PC2, corroborating the relationship between craving and CUD severity. Conclusions These results indicate that neural activity primarily underlies response to cannabis cues and that a complex relationship characterizes a convergent neural response and a divergent subjective craving response that differs between the sexes. Accounting for these differences will increase efficacy of treatments through personalized approaches.

2020 Caulkins et al looked at the intensity of use in the findings of three online surveys. Drug use is often measured in terms of prevalence, meaning the number of people who used any amount in the last month or year, but measuring the quantity consumed is critical for making informed regulatory decisions and estimating the effects of policy changes. Quantity is the product of frequency (e.g., number of use days in the last month) and intensity (amount consumed per use day). Presently, there is imperfect understanding of the extent to which more frequent users also consume more intensively. Methods and data We examine cannabis flower consumption reported in three similar online surveys fielded in times and places where cannabis was and was not legal. These convenience samples returned enough valid responses ($n = 2,618$) to examine consumption across different frequencies of use via analyses of measures of central tendency, data visualizations, and multivariate regressions. Additional calculations incorporate data from the National Survey on Drug Use and Health. Findings. Respondents who reported using daily (i.e., 30 days in the past month) consumed almost twice as much per day of use on average as did those reporting less than daily. We find only modest increases in intensity among those using less than daily, but then a substantial increase ($p< 0.001$) for those who use daily. Most respondents report that on heavy or light use days their consumption differs from a typical day of use by a factor of 2 or more, but only about 25% of days were described as heavy or light. We estimate those using cannabis 21+ days a month account for 80% of consumption vs. 71% of the days of use.

2020 Silver et al investigated the Assessment of Incorporation of Lessons From Tobacco Control in City and County Laws Regulating Legal Marijuana in California. California legalized medical marijuana in 1996 and adult recreational use in 2016, effective in January 2018. A cross-sectional study with data collection and analysis from February 1 to November 30, 2019, measured the adoption of potential demand reduction and youth protection best practices, including restrictions on sales, products, marketing, warnings, and taxation. Laws in effect by January 31, 2019, were verified and all 539 California local jurisdictions were studied. **Main Outcomes and Measures** Adoption of potential best practices in marijuana laws for demand reduction and youth protection. **Results** The laws of 534 of California's 539 jurisdictions (99%) were successfully identified; 263 of these 534 jurisdictions (49%) allowed any retail sale of marijuana, covering 57% of the state's population. More than one-third of jurisdictions allow sales of marijuana for adult recreational use (203 of 534 [38%]); of those, 122 allow storefront dispensaries and 81 allow sales by delivery only. A total of 257 of 534 jurisdictions (48%) allow medical sales. Of 147 jurisdictions allowing medical or adult use dispensaries, 93 (63%) limited the number of licenses, with a mean of 1 store for every 19 058 residents (range, 154-355 143). The state imposed no limits on number of dispensaries or deliverers. Forty-two jurisdictions increased the state-specified distances required between dispensaries and schools. Only 8 jurisdictions allowing retail sales imposed restrictions on products exceeding state regulations; 1 prohibited sale of flavored products, 3 prohibited sale of marijuana-infused beverages, and 5 imposed additional restrictions on edible marijuana products. No jurisdictions limited potency of products sold, although 1 established a potency-linked tax. The state did not limit or tax potency, except for establishing a standard 10-mg dose of tetrahydrocannabinol for edible marijuana products, nor did they limit manufacturing or sale of flavored products. The state required only a health warning in 6-point font on packages. Twenty-seven jurisdictions required additional health warnings in stores or on packages, 27 allowed onsite consumption of marijuana products, and 13 allowed marijuana-related events. More than half of jurisdictions legalizing any cannabis commerce (154 of 289 [53%]) did not tax marijuana locally and little revenue was captured for prevention. Much of the state excise and cultivation taxes is slated for youth substance use prevention and treatment. **Conclusions and Relevance** In implementing legalization of marijuana in California, local policies varied widely. Where marijuana was legalized, many lessons from tobacco control to reduce demand, limit harm, and prevent youth use were not adopted, potentially creating greater risk of harm.

2020 Hiller-Sturnhoefel found that parent's marijuana use may increase children's risk of marijuana use and favourable views of mariuana. This study found: Children's risk of marijuana and alcohol use and attitudes toward marijuana were influenced by their parents' marijuana use pattern over time. Children whose parents used marijuana primarily during adolescence/early adulthood and those whose parents continued to use marijuana from adolescence through adulthood were at highest risk.

2020 Marmet et al looked at cannabis use disorder trajectories and their prospective predictors in a large population-based sample of young Swiss men. Cannabis use disorder (CUD) is frequent in adolescence and often goes into remission towards adulthood. This study aimed to estimate trajectories of CUD severity (CUDS) in Swiss men from 20 to 25 years old and to identify prospective predictors of these trajectories. **Design** Latent class growth analysis of self-reported CUDS in a cohort study with three data collection waves. **Setting** A general population sample of young Swiss men.5987 Swiss men assessed longitudinally at the mean ages of 20, 21.5 and 25 years old. **Measurements** Latent CUDS in the last 12 months was measured at each wave with the Cannabis Use Disorders Identification Test Revised (CUDIT-R). Predictors of CUDS trajectories, measured at age 20, were from six domains: factors related to cannabis use, family, peers, other substance use, mental health and personality. **Findings** We distinguished four CUDS trajectories: stable-low (88.2%), decreasing (5.2%), stable-high (2.6%) and increasing (4.0%). Predictors were generally associated with higher odds of membership in the decreasing and stable-high trajectory (vs. the stable-low), and to a lesser degree with higher odds of membership in the increasing trajectory. Bivariate predictors of persistent high CUDS (stable-high vs. decreasing trajectory) were major depression severity (OR [95% CI]: 1.19 [1.01, 1.40]), attention deficit hyperactivity disorder severity (1.25 [1.04, 1.51]), antisocial personality disorder severity, relationship with parents (0.74 [0.63, 0.88]), number of friends with drug problems (1.33 [1.11, 1.60]) and the personality dimensions neuroticism-anxiety (1.35 [1.11, 1.65]) and sociability (0.78 [0.62, 0.97]). **Conclusions** Factors associated with persistent cannabis use disorder in young Swiss men include cannabis use, cannabis use disorder severity, mental health problem severity, relationship with parents (before the age of 18), peers with drug problems, and the personality dimensions neuroticism-anxiety and sociability at or before age 20. Effect sizes may be small and predictors are mainly associated with persistence via higher severity at age 20.

2020 Lancet: Organised Crime. The missing Link in Drug Policies. Illegal drugs and their effect on public health were discussed in a 2019 *Lancet* Series. However, the Series authors did not report how a global criminal enterprise, the drug–abuse industrial complex, is the origin of the problem. This global network of organised crime, corrupt politicians, money laundering, and distribution systems perpetuates this public health crisis. We have reason to believe the drug trade is now expanding under the guise of legal cannabis

and cannabidiol, especially in North America, with outreach to other markets in South America, Europe, and Asia. The Dutch police released a report stating that the growth of organised crime is creating a narco-state. Drug policies should consider organised crime or they will be unable to address the prevention and reduction of both drug use and crimes related to drug use from the perspectives of both public health and law enforcement. The Netherlands has, in a sense, created the perfect environment for the drug trade to flourish. The country has an extensive transport network, lenient drug laws, and proximity to a number of lucrative markets.Thus, the Netherlands is an obvious hub for the flow of global narcotics. If health professionals, researchers, and policy makers choose to leave organised crime aside in the discussion, we will pay a heavy price. Organised crime is the cause of the drug-abuse crisis in society. Decades of drug policy have been limited by ignoring organised crime, and it should be included in future discussions on drug policy.

2020 Weinberger et al investigated cannabis use among US adults with anxiety from 2008 to 2017. Abstract Cannabis use is more common among adults with anxiety. Cannabis legalization is occurring rapidly across the United States (US) and individuals may use cannabis to cope with anxiety. This study investigated whether cannabis use across the US has changed differentially by anxiety status and by state cannabis legalization for medical (MML) and/or recreational use (RML). Methods Public and restricted-use data from the 2004-2017 National Survey on Drug Use and Health, an annual cross-sectional, nationally representative survey of US individuals, were analyzed. The prevalence of past-30-day cannabis use by anxiety status in 2017 was estimated among respondents ages ≥18 (n = 42,554) by sociodemographics and state-level cannabis law. Weighted logistic regressions with continuous year as the predictor for the linear time trend were used to examine the time trends in cannabis use by anxiety and cannabis law status from 2004 to 2017 (total combined analytic sample n = 398,967).Results Cannabis use was consistently two to three times higher among those with high anxiety compared to those with some or no anxiety and was higher in states with RML compared to MML or no MML/RML. Conclusion: Cannabis use has increased over time among those with and without anxiety overall, in MML states, and in states without MML/RML; with a faster increase in cannabis use among those with high anxiety compared to lower anxiety in states with MML. Cannabis use is increasing among American adults overall, yet is disproportionately common among Americans with anxiety especially among those residing in states where cannabis has been legalized.

2020 Hasin et al looked at US adults with pain, a group increasingly vvulnerable to non-medical annabis use and cannabis use disorder 2001 – 2002 and 2012- Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, 2001–2002; N=43,093) and NESARC-III (2012–2013; N=36,309) were analyzed using logistic regression. Risk differences of past-year nonmedical cannabis use, frequent (at least three times a week) nonmedical use, and DSM-IV cannabis use disorder were estimated for groups with and without moderate to severe pain, and these risk differences were tested for change over time. Results: Any nonmedical cannabis use was more prevalent in respondents with than without pain (2001–2002: 5.15% compared with 3.74%; 2012–2013: 12.42% compared with 9.02%), a risk difference significantly greater in the 2012–2013 data than in the 2001–2002 data. The prevalence of frequent nonmedical cannabis use did not differ by pain status in the 2001–2002 survey, but was significantly more prevalent in those with than without pain in the 2012–2013 survey (5.03% compared with 3.45%). Cannabis use disorder was more prevalent in respondents with than without pain (2001–2002: 1.77% compared with 1.35%; 2012–2013: 4.18% compared with 2.74%), a significantly greater risk difference in the data from 2012–2013 than from 2001–2002. Conclusions: The results suggest that adults with pain are a group increasingly vulnerable to adverse cannabis use outcomes, warranting clinical and public health attention to this risk. Psychiatrists and other health care providers treating patients with pain should monitor such patients for signs and symptoms of cannabis use disorder.

2019 Chandra et al looked at nw trends in cannabis potency in USA and Europe during the last decade 2008-2017. Through the potency monitoring program at the University of Mississippi supported by National Institute on Drug Abuse (NIDA), a total of 18108 samples of cannabis preparations have been analyzed over the last decade, using a validated GC/FID method. The samples are classified as sinsemilla, marijuana, ditchweed, hashish, and hash oil (now referred to as cannabis concentrate). The number of samples received over the last 5 years has decreased dramatically due to the legalization of marijuana either for medical or for recreational purposes in many US states. The results showed that the mean Δ9-THC concentration has increased dramatically over the last 10 years, from 8.9% in 2008 to 17.1% in 2017. The mean Δ9-THC:CBD ratio also rose substantially from 23 in 2008 to 104 in 2017. There was also marked increase in the proportion of hash oil samples (concentrates) seized (0.5-4.7%) and their mean Δ9-THC concentration (6.7-55.7%) from 2008 to 2017. Other potency monitoring programs are also present in several European countries such as The Netherlands, United Kingdom, France, and Italy. These

programs have also documented increases in Δ9-THC concentrations and Δ9-THC:CBD ratios in cannabis. These trends in the last decade suggest that cannabis is becoming an increasingly harmful product in the USA and Europe.

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Cannabis and the Cardiovascular system

Comparatively little research has been done in this area, but there are sufficient published scientific papers to raise concern.

At first the intoxication produced by cannabis causes an increase in heart rate of between 20 and 50% (Huber et al 1988, Jones 1984). A rise in blood pressure occurs if the person is sitting or lying, but on standing up the pressure drops, in some cases causing the person to faint (Maykut 1984). A new and naive smoker may be concerned about these effects (Sidney 2002), but someone with a healthy heart is not thought to be at risk.

Cannabis affects the cardiovascular system in other ways as well. THC increases the production of chemicals called catecholamines which stimulate the heart, it also has analgesic properties which may lessen any chest pain and delay the seeking of treatment and the level of carboxyhaemoglobin is raised, decreasing the supply of oxygen to the heart, placing it under greater strain (Jones 1982 and 1984).

Older field studies involving chronic cannabis users in Costa Rica (Carter et al 1980), Greece (Stefanis et al 1977) and Jamaica (Rubin and Comitas 1975), found no evidence of cardiac toxicity even in subjects with existing heart disease. And electrocardiographic studies in both acute and prolonged administration have rarely revealed pathological changes (Benowitz and Jones1975, Jones 1984). So again it was concluded that young healthy adults using cannabis intermittently ran no major risk of a life-threatening cardiovascular event as may occur with a drug like cocaine. (Gawin, Ellinwood 1988).

However tolerance quickly develops to the acute cardiovascular effects of cannabis (Benowitz and Jones 1975, Jones and Benowitz 1976, Nowlan and Cohen 1977). And Jones (1984) showed that in people receiving daily high doses by mouth, tolerance develops in 7 to 10 days. This could possibly help to explain why toxic effects are sometimes not seen.

More recently though, there have been a number of papers documenting myocardial infarction and angina pectoris among young people using cannabis.

Podczeck and others 1990 reported 2 cases of myocardial infarction in very young healthy people and Choi and Perl 1989 and Perl and Choi 1992 found the same in young men, heavy users, with no history of heart disease. In 2000 Kosior and others wrote about 2 cases of cardiac arrhythmia (one of atrial fibrillation and one of recurrent paroxysmal tachycardia) in youngsters. Jones in 2002 reported transient ischaemic attacks and strokes in young and older people as well as deaths in young people from myocardial infarction.

Three teenagers, 15,16 and 17, who “binge smoked” cannabis suffered strokes, two died and one was left paralysed. In the two who died the stroke appeared to have been triggered by a clot in the brain or a constriction of the blood vessels over a wide area (Geller et al 2004). Professor John Henry of Imperial College said it was very disturbing, “I have seen cases of stroke due to cannabis use but fortunately none of my patients have died. One woman had all the signs of a stroke with paralysis down one side but fortunately recovered after several days”.

A 36 year-old man suffered strokes on three separate occasions, at almost yearly intervals, shortly after smoking a large amount of cannabis. He had been an occasional cannabis user, did not use other drugs and drank only occasionally. He had no known risk factors for stroke and no narrowing or hardening of the arteries which may lead to strokes or heart attacks. Mateo et al in 2005 said, “…even if the side effect is rare, it is a serious one”

An item in The Crawley News (Trinity Mirror PLC) on 12/07/06 reported that a 23-year-old sales manager had collapsed and died from a brain haemorrhage. He was a fit, healthy man with no hardening of the brain arteries but had a history of cannabis abuse and had been complaining of headaches for some time. At the inquest, Dr Colin Hunter-Craig said, “ He died of a brain haemorrhage due to cannabis abuse…This is incredibly rare in young people, but in old people we would recognise this as a stroke”.

Research in 2001 by Herning et al using Transcranial Doppler Sonography (Sound waves to measure cerebral artery blood flow resistance) found that prolonged marijuana use in 18 to 30 year olds increased the resistance in these arteries so restricting blood flow to the brain. 16 long-term male users were

compared with 19 non-users. The deficit persisted for 4 weeks after abstinence. They compared the results to that of the brain of a 60 year old. Advancing age increases the chance of a stroke.

Mittleman and others in 2001 interviewed 3882 patients with heart attacks. He concluded that the risk of onset of myocardial infarction rose by almost 5 times in the hour following the smoking of a joint.

2002 Clinical Cardiology carried an article by McLeod L et al on myocardial infarction in a young man following the combined use of cannabis and viagra. Viagra is metabolised predominantly by cytochrome P450 3A4 isoenzyme. Cannabis is a known inhibitor of this isoenzyme. Caution is needed in prescribing viagra in cases where the person has cardiovascular disease because of the vasodilatory effects of viagra.

In January 2004 an article in Neurologist by Moussouttas reviewed all reported cases of presumed cannabis related cerebral ischemic events in the medical literature, as well as pertinent human and animal experimental studies on the cardiovascular and cerebrovascular effects of cannabis. His conclusion was "Cannabis use seems to have been causally related to several instances of cerebral ischemia and infarction. Proposed etiologic mechanisms have included cerebral vasospasm, cardio-embolization and systematic hypotension with impaired cerebral auto-regulation, but most of the available data points to a vaso-spastic process. The exact relation to cerebro-vascular disease remains to be determined".

We still do not know the long term effects of exposure to cannabis smoke on the cardiovascular system over several years but our experiences with the problems of tobacco smoke should make us very cautious. Jones (1984) suggested that, "after years of repeated exposure, there may be lasting, perhaps even permanent alterations of the cardiovascular system function". He says, " There are enough similarities between THC and nicotine's cardiovascular effects to make the possibility plausible".

One paper in 2004 involving a study on genetically modified mice found that THC helped prevent atherosclerosis, a "furring up" of the arteries caused by plaques of protein and other material. The study was headed by Francois Mach a cardiologist, and published in Nature. He warned that smoking cannabis would not be the answer as oxygen levels are reduced and THC increases the heart rate and interferes with blood pressure as previously described. He called for THC (already available as a medicine, Nabilone) or other cannabinoid derivates to be investigated for this role. This is in line with all licensed medicines that must be pure single chemicals and subjected to standard clinical testing. This request was repeated in another paper by Mach and Steffens in January 2006.

In 2005 a letter to the editor of The International Journal of Cardiology was sent by Lindsay et al. It described 2 distinct cases giving cause for concern. In the first, "cannabis use precipitated a malignant arrhythmia in a patient with critical ischaemia from long-standing coronary artery disease. In the second, a young patient presented with an acute myocardial infarction that had started while smoking marijuana; subsequently diffuse coronary artery disease was found at angiography despite the patient's low risk factor status".

A case of paroxysmal artrial fibrillation (AF), a common condition usually triggered by alcohol use, was documented when a young female 22 year old presented herself. She had normal echocardiography but was a regular daily (1-2 joints) cannabis smoker. The author, Charbonney in 2005, warned that marijuana was a unusual trigger but should be checked for in young people after alcohol consumption had been ruled out.

The Irish Examiner on 3rd May 2007 reported the sudden death of a 21 year-old fit young father. Tiny traces of cannabis were found in his system. Assistant state pathologist, Dr Margaret Bolster said David Kelly died because the rhythmical electrical pulse in his heart misfired, causing it to stop. She pointed to a growing body of medical evidence which shows links between the triggering of similar heart conditions and the use of drugs like cannabis and cocaine. The individual may have had an underlying genetic cardiac problem, this happens in almost a quarter of such cases.

A study in February 2008 on atrial fibrillation and marijuana smoking by Korantzopoulos et al links atrial fibrillation with marijuana smoking. Only healthy young male smokers took part and it was found that "Compelling evidence is accumulating that cannabis has significant haemodynamic (change in blood pressure) and electrophysiological (tachycardia and atrial fibrillation) effects on the cardiovascular system". The authors concluded that atrial fibrillation should be included in the cardiovascular complications of marijuana smoking. Its incidence in the general population is probably underestimated.

A 2008 paper by Mukamal et al found that marijuana use was associated with a 3-fold greater mortality after acute myocardial infarction. This suggests there may be particular risks for people with established cardiovascular disease.

2008 A possible connection between marijuana abuse and stokes or heart attacks was found in a paper in 2008 (May) by Jayanthi and others. Abnormalities in proteins caused by heavy marijuana use were investigated. A protein, apoC -111 (apolipoprotein C-111) showed significant increases in marijuana users. This is associated with increases in triglycerides. This may be one reason why some marijuana users have an increased risk of stroke and heart attack.

2010 Jouanjus et al looked at cannabis-related hospitalizations among 200 patients admitted to the public hospitals of the Toulouse area of France between Jan 2004 and Dec 2007. They found that one of the adverse events (AE) was lethal. Psychiatric disorders occurred in 57.7%, leading to 18.2% of AEs, central and peripheral nervous system disorders, 15.8%, acute intoxication 12.1%, respiratory system disorders 11.1%, and cardiovascular disorders 9.5%.

2011 April Wolff et al examined 48 consecutive young patients admitted for acute ischemic stroke. They found multifocal intracranial stenosis associated with cannabis use in 21% (10 patients), and cocluded that multifocal angiopathy associated with cannabis consumption could be an important cause of ischemic stroke in young people.

2013 February Wolff, after a new literature review, concluded that cannabis-related stroke is not a myth and cannabis use should be considered as a risk factor inducing ischemic stroke. She said, 'most cannabis users are young , patients under 45 years of age presenting with symptoms of stroke should be asked about cannabis use and their urine tested for cannabinoids. 59 cases of cannabis-related stroke (mean age 33) were describedmostly male ratio male to female 4.9:1. Of the 59, 46 were classified as ischemic stroke, 5 were transient ischemic attacks, one a haeorrhagic stroke and in 4 patients a diagnosis of stroke was suspected but no neuro-imaging was done. In many cases they occurred while smoking or within half an hour.

2013 February 6th Dr Alan Barber (University of Auckland) presented his findings to The American Stroke Association annual meeting in Honolulu. He studied 160 controls and 160 stroke patients, 150 of them with ischemic strokes. 16% of stroke patients had positive cannabis screens compared with only 8% of the controls. This is a doubling of the risk. They were more likely to be male (84%) and tobacco smokers (88%). This is a doubling of the risk for cannabis users.

2013 Professor Joseph Harbison told Dublin Coroner's Court that St James's Hospital had seen 5 or 6 cases of young people having strokes following the use of herbal cannabis in the last 3 years. He thought it may be due to the higher strength.

2014 Thomas et al determined what cardiologists need to know. 200 million use cannabis worldwide. Since cannabis is now legal in 2 American States and medical cannabis is available in around 20 others, it is important that cardiologists are aware of the increase in health problems that may occur. These are: myocardial infarction, sudden cardiac death, cardiomyopathy, stroke, transient ischemic attacks, and cannabis arteritis.

2014 Singh and others Looked at a case of atrial fibrillation in an eighteen year old adolescent. An 18 year old with a structurally normal heart presented with prolonged atrial fibrillation (AF) precipitated by new-onset generalised tonic-clonic convulsions and marijuana abuse. This is an interesting association and a unique pathophysiology between generalised toni-clonic convulsions , marijuana abuse and AF. Seizures and marijuana abuse should be considered in the differential diagnosis of the etiology of AF in children.

2014 Daldrup et al found that 2 young men had died unexpectedly after smoking cannabis. A 23 year old had a serious undetected heart problem and the 28 year old had abused alcohol, amphetamine and cocaine in the past. 'To our knowledge these are the first cases of suspected fatal cannabis intoxications where full post-mortem investigations…… were carried out'.

2014 Jouanjus et al, looked at all spontaneous reports of cardiovascular complications related to cannabis use collected by the French Addictovigilance Network from 2006 to 2010. 1.8% of all cannabis-related reports (35/1979) were cardiovascular complications, with patients being mostly men (85.7%) and of an average age of 34.3 years. There were 22 cardiac complications (20 acute coronary syndromes), 10

peripheral complications (lower limb or juvenile arteriopathies and Buerger-like diseases), and 3 cerebral complications (acute cerebral angiopathy, transient cortical blindness, and spasm of cerebral artery). In 9 cases, the event led to patient death.

2014 April Casier et al reported cases of 3 patients where recent and/or chronic use of marijuana lead to severe cardiac function. All 3 collapsed at home and needed CPR with initial restoration of spontaneous circulation (ROSC). All 3 had used cannabis and no other drug. They concluded: ' Cannabis use can lead to severe cardiovascular problems and sudden death, not only in people at increased cardiovascular risk but also in young people without any medical history or risk factors'.

2014 Lee found migratory superficial thrombophlebitis in a cannabis smoker. A 28-year old man had a 5-year history of recurrent painful subcutaneous nodules in various parts of his body. He developed a 1cm nodule in his right calf which progressed over 2 days to 4cm. This was repeated once/every few weeks in diffeent locations. This was Buerger disease. Tobacco smoking is often considered essential but he denied smoking. A few cases associated with cannabis have been repported.

2014 Wolff and others looked at the high frequency of intracranial arterial stenosis and cannabis use in ischaemic stroke in the young. 159 patients (18-45) admitted for acute ischaemic stroke from Oct 2005 to Dec 2010 were studied. Conclusion: Intracranial arterial stenosis may be an important mechanism of stroke in young patients and should be systematically investigated using vascular imaging. Patients should be strongly questioned about cannabis use. Cannabis use may be associated with critical consequences such as stroke.

2014 Gunawardena et al reported a case of myocardial infarction following cannabis induced vasospasm. A 29 year old man (Sri Lanka) presented with acute coronary syndrome following consumption of 'Kerala Ganja', a much more potent form than the local ganja (marijuana). A diagnosis was made of vasospasm causinf myocardial infarction, most likely to have been triggered by cannabis consumption.

2014 Wang et al looked at the damage to blood vessels by secondhand marijuana smoke. Anaesthetised rats were exposed to marijuana SHS (Secondhand smoke). They concluded that marijuana and tobacco SHS impair endothelial function similarly under comparible exposure conditions. Public exposure should be avoided whether tobacco or marijuana smoke.

2015 Hackam investigated cannabis and strokes. Case reports on cannabis and cerebro-vascular events were retrieved. There were 34 case reports on 64 patients. Most of them (81%)exhibited a temporal relationship between cannabis exposure and the index event. In 70% the evaluation was sufficiently comprehensive to exclude other sources for stroke. 22% of the patients had another stroke after subsequent re-exposure to cannabis. Finally half the patients had concominant stroke risk factors, most commonly tobacco (34%) and alcohol (11%) consumption. They concluded that many case reports support a causal link between cannabis and cerebro-vascular events.

2015 Rumalla et al looked at hospitalizations for aneurismal sub-arachnoid haemorrhage (aSAH). The Nationwide Inpatient Sample, 2004-2011 was used. They concluded that 'Our analysis suggests that recreational cannabis use is independently associated with an 18% increase likelihood of asAH'. It was more frequent in younger male patients.

2016 Wang et al looked at second-hand marijuana smoke (SHS) exposure and vascular endothelium functioning. Endothelial function was measured as femoral artery flow-mediated dilation (FMD) in rats. One minute of exposure to SHS of marijuana impaired FMD to a comparable extent as impairment from equal concentrations of tobacco SHS but recovery was considerably slower.

2016 Singh et al found that marijuana use may be linked to temporarily weakened heart muscle. 'Active marijuana use may double the risk of stress cardiomyopathy , an uncommon heart muscle malfunction that can mimic heart attack symptoms'. The heart's ability to pump leads to chest pain, shortness of breath, dizziness and sometimes fainting. 33,343 people hospitalised with the condition from 2003-2011 in the USA were studied. Less than 1% were cannabis users (210). These users were significantly more likely to go into cardiac arrest (2.4% v 0.8% (non-users), and require a defibrillator. "Marijuana users were more likely than non-users to have a history of depression (32.9 percent vs. 14.5 percent), psychosis (11.9 percent vs. 3.8 percent), anxiety disorder (28.4 percent vs. 16.2 percent), alcoholism (13.3 percent vs. 2.8 percent), tobacco use (73.3 percent vs. 28.6 percent) and multiple substance abuse (11.4 percent vs. 0.3

percent). Because some of these can increase the risk of stress cardiomyopathy, the researchers adjusted for known risk factors to investigate the association between marijuana use and stress cardiomyopathy."

2016 Reece and others looked at cannabis exposure as an interactive cardiovascular risk factor and accelerant of organismal ageing. 11 cannabis-only smokers, 504 tobacco-only users, 114 tobacco and cannabis users and 534 non-smokers were studied over a 5 year period. They discovered that long-term use of cannabis increased the biological age of those studied by 11% due to the impact of hardening of the arteries e.g. a thirty year old would have a biological age of 33. Associate Professor Stuart Reece said that the results showed that, 'not only doesit age you, it increases ageing at an exponential rate over time which is alarming'.

2016 Draz et al Looked at marijuana use in acute coronary syndromes. 138 male patients, around 40 years of age with acute myocardial infarction were studied. Urine samples were submitted for toxicological analysis. None of group 1(cannabis positive only) had normal coronaries. Significant changes in echocardiography and angiography were found between group 1 and the other groups – group 2 (patients positive for other substance abuse) and group 3 (Negative for any substance abuse). 'Cannabis smoking could be a potential risk factor for the development of cardiac ischemia'.

2017 Kalla et al found that cannabis users have a 26% higher chance of suffering a stroke and 10% higher chance of suffering a heart attack than non-users. Confounding factors like obesity, alcohol and tobacco smoking were accounted for. Previous research in cell culture has shown that heart muscle has cannabis receptors relevant to contractility or squeezing ability which may be one mechanism whereby marijuana use could affect the cardiovascular system. More than 20 million records of young and middle-age patients between 18 and 55 discharged from 1,000 hospitals in 2009 and 2010 when marijuana use was illegal in most states were studied. 1.5% were marijuana users.

2017 Miech et al found that college attendance was a risk factor for cannabis use. 'Data come from the Monitoring the Future study, which has followed longitudinal panels drawn from annual nationally representative, baseline samples of 12th-grade students starting with the class of 1976. We studied panel members aged 19 to 22 years who had never used marijuana by 12th grade between 1977 and 2015. *Results.* College as a risk factor for marijuana initiation has increased significantly since 2013. The increased probability of past-year marijuana use for those enrolled versus not enrolled in college was 51% in 2015, 41% in 2014, and 31% in 2013; it averaged 17% to 22% from 1977 to 2012 among youths who had never used marijuana by 12th grade. Conclusin: College has grown as a risk factor for marijuana initiation since 2013'.

2017 Atchaneeyasakul et al found that a large amount of cannabis ingestion results in spontaneous intracerebral haemorrhage. Abstract: Although multiple cases of cannabis-associated ischemic stroke have been reported, there are only 2 reported cases of hemorrhagic stroke with an associated cerebral vasoconstriction. To our knowledge, we present the first case of basal ganglia hemorrhage after a large-volume oral ingestion of cannabis without other identified risk factors. In our case, cerebral digital subtraction angiography within 24 hours of presentation did not reveal vasoconstriction leading to a possible alternative explanation for hemorrhagic stroke, including cannabis-induced transient arterial hypertension and auto-regulation disruption'.

2017 Wolff et al found that strokes are possible combinations of cannabinoid use. Ninety eight patients were described as cannabinoid-related stroke, 85 after cannabis use and 13 after synthetic cannabinoids. The mean age of patients was 32.3 years and ratio of male to female was 3.7:1. In 66% of cases cannabis was smoked with tobacco. Most with cannabinoid strokes were chronic (81%) cannabis users and for 18% of them there had been an increase in consumption of cannabis in the days before the stroke. The prognosis was favourable in 46% of cases, but 5 patients died. As of today, reversible cerebral vasoconstriction triggered by cannabinoid use may be a convincing mechanism of stroke in 27% of all cases.

2017 Yankee et al looked at the effect of marijuana use on cardiovascular and cerebrovascular mortality. 'The design of this study was based on a mortality follow-up. Method We linked participants aged 20 years and above, who responded to questions on marijuana use during the 2005 US National Health and Nutrition Examination Survey to data from the 2011 public-use linked mortality file of the National Center for Health Statistics, Centers for Disease Control and Prevention. Only participants eligible for mortality follow-up were included. We conducted Cox proportional hazards regression analyses to estimate hazard ratios for hypertension, heart disease, and cerebrovascular mortality due to marijuana use. We controlled for cigarette

smoking and other relevant variables. Results Of the 1213 eligible participants 72.5% were presumed to be alive. The total follow-up time was 19,569 person-years. Adjusted hazard ratios for death from hypertension among marijuana users compared to non-marijuana users was 3.42 (95% confidence interval: 1.20-9.79) and for each year of marijuana use was 1.04 (95% confidence interval: 1.00-1.07). Conclusion From our results, marijuana use may increase the risk for hypertension mortality. Increased duration of marijuana use is associated with increased risk of death from hypertension. Recreational marijuana use potentially has cardiovascular adverse effects which needs further investigation'.

2017 Volcon et al looked at multiple cerebral infarcts in a young patient associated with marijuana use. ' Cerebrovascular events associated with marijuana use have been reported previously. This association is plausible, but not well-established yet. A 14-year-old girl, long-term heavy cannabis user, presented with generalized tonic-clonic seizures and decreased level of consciousness a few hours after smoking cannabis. Brain magnetic resonance imaging showed multiple areas of acute, subacute and chronic ischemic lesions in the left frontal lobe, basal ganglia, and corpus callosum. History of other illicit drug use and other known causes of stroke were ruled out. Cannabis might cause stroke through direct effects on the cerebral blood circulation, orthostatic hypotension, vasculitis, vasospasm, and atrial fibrillation. Long-term daily use of marijuana in young people may cause serious damage to the cerebrovascular system'.

2017 Rickner et al looked at a case report of neuro-and cardiotoxicity following use of cannabis concentrates. 'A 17-year-old athletic man developed agitation requiring sedation and intubation for safety, with peak systolic blood pressures in the 190s and hyperthermia (to 102 °F). He developed elevated serum troponins with persistent tachycardia despite sedation and no clear non-intoxicant etiology. It was discovered that the patient had recently been "dabbing"; an exhaustive search of his home found a sample of the "dabs" which was analyzed along with a comprehensive urine drug screen by tandem liquid mass spectroscopy (t-LCMS) for confirmation.Tetrahydrocannabinol (THC) has been increasingly associated with agitation and cardiotoxicity, while cannabidiol (CBD) has been associated with neuroprotective, inhibitory states. We propose that increasing concentrations of THC as well as THC:CBD ratios seen in cannabis concentrates such as "dabs" may cause agitation and end-organ damage through sympathomimetic and serotonergic pathways.

2017 Gomez-Ochoa investigated stroke and cannabis use in patients with no cardiovascular risk factors. 'A systematic literature review was conducted through Medline, EBSCOhost, EMBASE, Lilacs, and Scielo to gather case reports published before 13 May 2016 presenting patients with a diagnosis of CVD or transient ischaemic attack, a history of cannabinoid use, and no other cardiovascular risk factors A total of 18 case reports were selected from the 566 references found.There is a wide variety of reports of stroke associated with cannabis use in patients with no other risk factors. Noteworthy findings were presentation at young age and a strong temporal association, which place cannabis use as a potential risk factor for this population in line with the epidemiological and pathophysiological studies in this area.

2017 Abouk et al looked at the relationship between medical cannabis laws and cardiovascular deaths in the US. 'We analyze cardiac-related mortality data from the U.S. National Vital Statistics System for 1990-2014. We use difference-in-difference fixed-effects models to assess whether there are increased rates of cardiac-related mortality following passage of medical cannabis programs. We also analyze whether states with more liberal rules on dispensing cannabis show higher mortality rates. For men, there is a statistically significant 2.3% increase in the rate of cardiac death following passage. For women, there is a 1.3% increase that is also statistically significant. he effects increase or both men and women with age. The effects are also stronger in states with more a lax approach to cannabis dispensing'.

2017 Singh et al looked at cardiovascular complications with marijuana and other substances. 'Absract: The recreational use of cannabis has sharply increased in recent years in parallel with its legalization and decriminalization in several countries. Commonly, the traditional cannabis has been replaced by potent synthetic cannabinoids and cannabimimetics in various forms. Despite overwhelming public perception of the safety of these substances, an increasing number of serious cardiovascular adverse events have been reported in temporal relation to recreational cannabis use. These have included sudden cardiac death, vascular (coronary, cerebral and peripheral) events, arrhythmias and stress cardiomyopathy among others. Many of the victims of these events are relatively young men with few if any cardiovascular risk factors. However, there are reasons to believe that older individuals and those with risk factors for or established cardiovascular disease are at even higher danger of such events following exposure to cannabis. The pathophysiological basis of these events is not fully understood and likely encompasses a complex interaction between the active ingredients (particularly the major cannabinoid, Δ9-tetrahydrocannabinol), and the endo-cannabinoid system, autonomic nervous system, as well as other receptor and non-receptor mediated pathways. Other complicating factors include opposing physiologic effects of other cannabinoids

(predominantly cannabidiol), presence of regulatory proteins that act as metabolizing enzymes, binding molecules, or ligands, as well as functional polymorphisms of target receptors. Tolerance to the effects of cannabis may also develop on repeated exposures at least in part due to receptor downregulation or desensitization. Moreover, effects of cannabis may be enhanced or altered by concomitant use of other illicit drugs or medications used for treatment of established cardiovascular diseases. Regardless of these considerations, it is expected that the current cannabis epidemic would add significantly to the universal burden of cardiovascular diseases'.

2018 Desai et al looked at recreational marijuana use and myocardial infarction. Abstract: To our knowledge, this is the first ever study analyzing the lifetime odds of acute myocardial infarction (AMI) with marijuana use and the outcomes in AMI patients with versus without marijuana use. We queried the 2010-2014 National Inpatient Sample (NIS) database for 11-70-year-old AMI patients. Pearson Chi-square test for categorical variables and Student T-test for continuous variables were used to compare the baseline demographic and hospital characteristics between two groups (without vs. with marijuana) of AMI patients. The univariate and multivariate analyses were used to assess and compare the clinical outcomes between two groups. We used Cochran-Armitage test to measure the trends. All statistical analyses were executed by IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). We used weighted data to produce national estimates in our study. Results Out of 2,451,933 weighted hospitalized AMI patients, 35,771 patients with a history of marijuana and 2,416,162 patients without a history of marijuana use were identified. The AMI-marijuana group consisted more of younger, male, African American patients. The length of stay and mortality rate were lower in the AMI-marijuana group with more patients being discharged against medical advice. Multivariable analysis showed that marijuana use was a significant risk factor for AMI development when adjusted for age, sex, race (adjusted OR 1.079, 95% CI 1.065-1.093, p<0.001); adjusted for age, female, race, smoking, cocaine abuse (adjusted OR 1.041, 95% CI 1.027-1.054, p<0.001); and also when adjusted for age, female, race, payer status, smoking, cocaine abuse, amphetamine abuse and alcohol abuse (adjusted OR: 1.031, 95% CI: 1.018-1.045, p<0.001). Complications such as respiratory failure (OR 18.9, CI 15.6-23.0, p<0.001), cerebrovascular disease (OR 9.0, CI 7.0-11.7, p<0.001), cardiogenic shock (OR 6.0, CI 4.9-7.4, p<0.001), septicemia (OR 1.8, CI 1.5-2.2, p<0.001), and dysrhythmia (OR 1.8, CI 1.5-2.1, p<0.001) were independent predictors of mortality in AMI-marijuana group. Conclusion The lifetime AMI odds were increased in recreational marijuana users. Overall odds of mortality were not increased significantly in AMI-marijuana group. However, marijuana users showed higher trends of AMI prevalence and related mortality from 2010-2014. It is crucial to assess cardiovascular effects related to marijuana overuse and educate patients for the same.

2018 Defilippis et al investigated cocaine and marijuana use among young adults presenting with myocardial infarction. Abstract: We retrospectively analyzed records of patients presenting with a Type 1 MI at ≤50 years at two academic hospitals from 2000-2016. Substance abuse was determined by review of records for either patient-reported substance abuse during the week prior to MI or detection on toxicology screen. Vital status was identified by the Social Security Administration's Death Masterfile. Cause of death was adjudicated using electronic health records and death certificates. Cox modeling was performed for survival free from all-cause and cardiovascular death. 2097 patients had Type 1 MI (mean age 44±5.1 years, 19.3% female, 73% white) with median follow-up of 11.2 years (interquartile range: 7.3-14.2). Use of cocaine and/or marijuana was present in 224 (10.7%) patients; cocaine in 99 (4.7%) patients and marijuana in 125 (6.0%). Individuals with substance use had significantly lower rates of diabetes (14.7% versus 20.4%, p = 0.05) and hyperlipidemia (45.7% versus 60.8%, p < 0.001), but were significantly more likely to use tobacco (70.3% versus 49.1%, p < 0.001). The use of cocaine and/or marijuana was associated with significantly higher cardiovascular (HR 2.22; 95% CI 1.27 – 3.7, p=0.005) and all-cause mortality (HR 1.99; 95% CI 1.35 – 2.97, p=0.001) after adjusting for baseline covariates.Cocaine and/or marijuana use is present in 10% of patients with an MI at age ≤50 years and is associated with worse all-cause and cardiovascular mortality.

2018 Pacher et al looked at the cardiovascular effects of marijuana and synthetic cannabinoids. Abstract: Dysregulation of the endogenous lipid mediators endocannabinoids and their G-protein-coupled cannabinoid receptors 1 and 2 (CB1R and CB2R) has been implicated in a variety of cardiovascular pathologies. Activation of CB1R facilitates the development of cardiometabolic disease, whereas activation of CB2R (expressed primarily in immune cells) exerts anti-inflammatory effects. The psychoactive constituent of marijuana, Δ9-tetrahydrocannabinol (THC), is an agonist of both CB1R and CB2R, and exerts its psychoactive and adverse cardiovascular effects through the activation of CB1R in the central nervous and cardiovascular systems. The past decade has seen a nearly tenfold increase in the THC content of marijuana as well as the increased availability of highly potent synthetic cannabinoids for recreational use. These changes have been accompanied by the emergence of serious adverse cardiovascular events,

including myocardial infarction, cardiomyopathy, arrhythmias, stroke, and cardiac arrest. In this Review, we summarize the role of the endocannabinoid system in cardiovascular disease, and critically discuss the cardiovascular consequences of marijuana and synthetic cannabinoid use. With the legalization of marijuana for medicinal purposes and/or recreational use in many countries, physicians should be alert to the possibility that the use of marijuana or its potent synthetic analogues might be the underlying cause of severe cardiovascular events and pathologies.

2018 August. Desai et al looked at the burden of arrhythmia in recreational cannabis users. Absract: Marijuana or Cannabis is extensively used as a recreational substance globally. Case reports have reported cardiac arrhythmias immediately following recreational marijuana use. However, the burden of arrhythmias in hospitalized marijuana users have not been evaluated through prospective or cross-sectional studies. Therefore, we planned to measure temporal trends of the frequency of arrhythmias in hospitalized marijuana users using National Inpatient Sample (NIS) database in the United States. Highlights:

- •Total of 2.7% of recreational marijuana users developed arrhythmia with a steadily increasing trend from 2010 through 2014.
- •Atrial fibrillation was the most common subtype arrhythmia among hospitalized marijuana users.
- •The incidence of arrhythmia in male and female marijuana users nearly increased two-fold between 2010 and 2014.
- •The all-cause in-hospital mortality in marijuana users with arrhythmias increased from 3.7% in 2010 to 4.4% in 2014.

2018 Kalla et al found that cannabis use predicts risks of heart failure and cerebro -vascular accidents. Cannabis for medicinal and/or recreational purposes has been decriminalized in 28 states as of the 2016 election. In the remaining states, cannabis remains the most commonly used illicit drug. Cardiovascular effects of cannabis use are not well established due to a limited number of studies. We therefore utilized a large national database to examine the prevalence of cardiovascular risk factors and events amongst patients with cannabis use. Patients aged 18-55 years with cannabis use were identified in the National Inpatient Sample 2009-2010 database using the Ninth Revision of International Classification of Disease code 304.3. Demographics, risk factors, and cardiovascular event rates were collected on these patients and compared with general population data. Prevalence of heart failure, cerebrovascular accident (CVA), coronary artery disease, sudden cardiac death, and hypertension were significantly higher in patients with cannabis use. After multivariate regression adjusting for age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, tobacco use, and alcohol use, cannabis use remained an independent predictor of both heart failure (odds ratio=1.1, 1.03-1.18, P<0.01) and CVA (odds ratio=1.24, 1.14-1.34, P<0.001). CONCLUSION: Cannabis use independently predicted the risks of heart failure and CVA in individuals 18-55 years old. With continued legalization of cannabis, potential cardiovascular effects and their underlying mechanisms need to be further investigated.

2018 Amen et al looked at the patterns of regional cerebral blood flow as a function of age throughout the lifespan. A large psychiatric cohort of 31,227 individuals received brain SPECT at rest and during a concentration task for a total of 62,454 scans. ANOVA was done to identify the mean age trends over the course of the age range in this group, 0-105 years. A regression model in which brain SPECT regions of interest was used to predict chronological age (CA) was then utilized to derive brain estimated age (BEA). The difference between CA and BEA was calculated to determine increased brain aging in common disorders in our sample such as depression, dementia, substance use, and anxiety. Throughout the lifespan, variations in perfusion were observed in childhood, adolescence, and late life. Increased brain aging was seen in alcohol use, cannabis use, anxiety, bipolar, schizophrenia, attention-deficit/hyperactivity disorder, and in men. Brain SPECT can predict chronological age and this feature varies as a function of common psychiatric disorders.

2020 Khanji et al looked at the association between recreational cannabis use and cardiac structure and functioning. Regular cannabis use could affect the structure and function of the heart, indicates research* published in *JACC Cardiovascular Imaging*.Researchers analysed MRI images from the UK Biobank population study and found an association between regular cannabis use and an enlarged left ventricle, together with early signs of impairment of heart function.The scans came from 3,407 individuals with an average age of 62 who did not have cardiovascular disease. Most (3,255) rarely or never used cannabis, 105 had used it regularly but more than five years before they were interviewed and 47 were current regular users.The latter group were more likely to have larger left ventricles and show early signs of impaired heart function, measured by how the heart muscle fibres deform during contraction. However, there appeared to be no difference between the three groups in the overall mass of the left ventricle or the amount of blood ejected with each heartbeat. No changes were identified in the size and function of the other three chambers of the heart.The analysis also found that people who had used cannabis regularly but given up had similar

heart size and function to those who had rarely or never taken the drug. Lead author Dr Mohammed Khanji, senior clinical lecturer at Queen Mary University of London, said: "We believe this is the first study to systematically report changes in heart structure and function associated with recreational cannabis using cardiac MRI, which is a very sensitive imaging tool and the current reference standard for assessing cardiac chambers. The World Health Organisation has warned about the potential harmful health effects of non-medical cannabis use and called for more research specifically around the cardiac impact."Dr Khanji, who is also a consultant cardiologist at Barts Health NHS Trust, added that with decriminalisation and legalisation of recreational cannabis use in many countries, systematic research is urgently needed to identify the long-term implications of regular consumption of cannabis on the heart and blood vessels. “This would allow health professionals and policymakers to improve advice to patients and the wider public," he said.

2020 Kruger et al looked at cannabis enthusiasts’ knowledge of medical treatment effectiveness and increased risks of cannabis use.PURPOSE:To compare cannabis enthusiasts' knowledge about cannabis risks and effectiveness in treating medical conditions with existing empirical evidence. DESIGN:A brief survey assessed cannabis use, information sources, and knowledge about risks and effectiveness.SETTING:A cannabis advocacy event in April 2019 in a state with legal medical and recreational cannabis.PARTICIPANTS:Demographically diverse adults (N = 472) who frequently used cannabis; 85% used cannabis for health or medical purposes.MEASURES:Participants reported the sources of their cannabis information, health conditions they thought cannabis was effective in treating (n = 10), and health risks increased by cannabis (n = 6). Conditions and risks were based on ratings of evidence (ie, from substantial to insufficient) for therapeutic effects and risks identified in a review by The National Academies of Sciences, Engineering, and Medicine (NASEM, 2017).ANALYSES:Chi-square tests examined the correspondence between participants' knowledge and NASEM conclusions. RESULTS:Most participants' (95% confidence interval [CI]: 74%-81%) knowledge of cannabis was from their own experiences; 18% (95% CI: 14%-21%) received information from primary care providers. On average, participants' beliefs matched NASEM conclusions for half of effectiveness (95% CI: 50%-53%) and risk items (95% CI: 55%-57%). Many (95% CI: 38%-42%) thought that cannabis use did not increase any risk. Contrary to NASEM conclusions, many thought cannabis was effective in treating cancer (76%), depressive symptoms (72%), and epilepsy (68%). Those who received cannabis information from their primary care providers had better knowledge of medical effectiveness. Medicinal cannabis use frequency inversely predicted knowledge of medical effectiveness and increased risks of adverse events.CONCLUSION:There were considerable discrepancies between cannabis users' knowledge and available evidence, highlighting the need for more research and education (by physicians, caregivers, and dispensaries) on effectiveness and health risks, especially for users with specific health issues such as pregnant women and people with depression.

2020 American Heart Association made a statement about medical marijuana, recreational cannabis, and cardiovascular health. Cannabis, or marijuana, has potential therapeutic and medicinal properties related to multiple compounds, particularly Δ-9-tetrahydrocannabinol and cannabidiol. Over the past 25 years, attitudes toward cannabis have evolved rapidly, with expanding legalization of medical and recreational use at the state level in the United States and recreational use nationally in Canada and Uruguay. As a result, the consumption of cannabis products is increasing considerably, particularly among youth. Our understanding of the safety and efficacy of cannabis has been limited by decades of worldwide illegality and continues to be limited in the United States by the ongoing classification of cannabis as a Schedule 1 controlled substance. These shifts in cannabis use require clinicians to understand conflicting laws, health implications, and therapeutic possibilities. Cannabis may have therapeutic benefits, but few are cardiovascular in nature. Conversely, many of the concerning health implications of cannabis include cardiovascular diseases, although they may be mediated by mechanisms of delivery. This statement critically reviews the use of medicinal and recreational cannabis from a clinical but also a policy and public health perspective by evaluating its safety and efficacy profile, particularly in relationship to cardiovascular health.

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Cannabis and its Effects on the Immune System

Since crude cannabis often contains various species of pathogenic fungi and bacteria it is important to establish the effects of cannabis smoking on the immune system.

The immune system exhibits a complex array of responses. Innate responses involve macrophages, important in engulfing and destroying foreign matter and natural killer cells, morphologically like lymphocytes, they bind to target cells and insert destructive granules into them.

Acquired immunity consists of lymphocytes.
B cells are responsible for the production of antibodies in "humoral immunity". T cells carry out "cell-mediated immunity". Activated T-lymphocytes act as cytotoxic cells and/or release substances which activate monocytes (the forerunners of macrophages) and macrophages.

Early research into the immune system was documented in the 1981/82 WHO Report into the adverse effects of cannabis.

Experimental animals consistently produced evidence that THC or marijuana administered parenterally or by inhalation resulted in immunological defects in mice and rats, rats being the more sensitive (Munson and Fehr 1982). These defects included decreased antibody responses and reduced lymphocyte proliferation. The cell-mediated immune suppression in mice was measured by a reduced response to bacteria, skin grafts and foreign cells, it also decreased lymphocyte proliferation. These results were obtained by THC doses which produced very little behaviour effects in the mice. However Smith and others in 1978 suggested that cannabinoids other than THC may contribute to the immuno-suppressive effects. Rosenkrantz in 1976, experimenting on rats found that THC significantly inhibits humoral (related to the production of antibodies) and cell-mediated (dependent on the presence of activated T-lymphocytes) immunity in the immune response of rats in a dose-related manner. A similar response was obtained by marijuana smoke from an automatic inhaler (controlled by THC-absent smoke). Doses equivalent to human consumption were used.

At that time Munson and Fehr found the evidence as to whether THC or marijuana can perturb monocyte or macrophage function to be mixed. It appeared that the effects were more pronounced if the cannabinoids were given in the early phase of antibody production (Luthra et al 1980) and were even more pronounced in young animals (Pruess and Lefkowitz 1978). Also up till 1981/82 there was no definite proof of immune dysfunction in human users of cannabis. Evidence was very contradictory (Munson and Fehr 1982). They

had looked at the numbers and functions of T and B-lymphocytes and macrophages. Serum immunoglobulin levels had also been investigated.

One study reported that the phagocytic ability of polymorphonuclear white blood cells was impaired (Petersen et al 1975) and another that there were biochemical and ultrastructural changes in the white blood cells of chronic hashish users (Stefanis and Issidorides 1976, Issidorides 1979).

Another approach to investigating a possible impairment of the immune system is to test the resistance of living organisms to infection. Cannabis-treated mice have shown a decreased resistance to infection by Listeria monocytogenes and Herpes simplex (Morahan and others 1979). In humans with dormant genital herpes, infections have been reactivated shortly after cannabis use (Juel-Jensen 1972). Other drugs which suppress the immune responses in mice also do the same in humans (WHO 1982).

A publication from the National Academy of Sciences, Institute of Medicine 1999, *Marijuana and Medicine: Assessing the Science Base*, gave an explanation of the problems encountered by human study researchers.

Blood leucocytes (white blood cells), isolated from people who have been smoking marijuana, used to evaluate the immune response in vitro almost always failed as the process involved high speed centrifugation and washing. This removed the cannabinoids (Kaklamani et al 1978, Lau et al 1976, Rachelefsky et al 1976 and White et al 1975).

Blood leucocytes from non-users can be used to test the effect of THC on their ability to proliferate in response to stimulation in vitro. The problem here is that marijuana smoke consists of many distinct cannabinoids, not just THC. At least one of the others, CBN (cannabinol) has greater activity on the immune system than on the CNS (Central Nervous System) (Herring and others 1998).

Another approach is to study human-derived cell lines. These lines can be treated with cannabis in vitro to test the responses to various stimuli. However subsequent cells may not be the same as the original one, eg not have the same number of cannabis receptors.

The late eighties saw a re-surgence in research on cannabis and the immune system, probably prompted by the spread of AIDS.

RH Schwartz in an article in The Journal of Hospital and Community Psychiatry 1987 wrote that marijuana use is a factor in preparing the ground for HIV infection.

In 1988 Hamadeh and his associates warned that, “Invasive Aspergillus (a fungus) has become a significant cause of death in immuno-suppressed patients. Physicians should be aware of this potentially lethal complication of marijuana use in compromised hosts such as patients with AIDS or malignancies”. Serious invasive fungal infections as a result of cannabis contamination have been reported among immunocompromised individuals including some with AIDS (Denning et al 1991).

In the same year, 1988, Tindall and others said that HIV positive marijuana smokers have an increased incidence of bacterial pneumonia compared to non-marijuana smokers, and added that marijuana smoking increases the progression to full-blown AIDS in HIV positive persons.

The fact that genital warts do not respond to systemic recombinant interferon alfa-2 treatment during cannabis consumption was discovered by Gross and others in 1991, and in 1994, Caiaffa and colleagues confirmed Tindall’s findings that marijuana smoking increases the incidence of bacterial pneumonias in AIDS patients.

A more recent study discovered that THC suppresses the immune function and enhances HIV replication in the hu PBL-SCID mouse. Exposure to THC in vivo can suppress the immune function, increase HIV co-receptor expression and act as a co-factor to significantly enhance HIV replication (Roth et al 2005).

Some hospital patients who had smoked 12 marijuana cigarettes a day for 4 days were found to have decreased antibody production in one type (IgG), Two other types of antibody were normal (IgA and IgM), and IgE was actually elevated (Nahas et al 1991).

Human mononuclear phagocyte cultures were treated with THC in vitro. There was a suppression of phagocyte function and also the spreading ability of macrophages. A metabolite of THC, 11-OH-THC, was found to reduce natural killer cell activity (Specter and Lantz 1991).

Cabral and others in 1991 carried out some experiments on rhesus monkeys. They subjected them to marijuana smoke in various groups for over a year then gave them a 7-month rest period. "High-dose" animals were given one marijuana cigarette a day, "low-dose" ones 1 marijuana cigarette for two consecutive days at weekends. Both groups had altered morphology of alveolar macrophages and protein expression. The cell surfaces were irregular and there was increased vacuolarization. Hosts thus affected could be at increased risk of infection.

THC is able to interfere with the functioning of white blood cells taken from humans. Both neutrophils which fight bacterial infection and mononuclear cells of the immune system which fight viruses were suppressed by various concentrations of THC (Djeu et al, Watzl et al, 1991).

In 1992 Cabral and Vasquez discovered that THC inhibited extrinsic but not intrinsic anti-herpes activity in a dose-dependent manner. This means that THC had no effect on the capacity of macrophage-like cells to take up the virus and no replication of the virus occurred inside the macrophage cells. However there was an inhibition of the macrophages to suppress viral replication in infected virus-susceptible cells. The action was reversible on removal of the drug.

In the same year Kaminski and others found that cannabis receptors CB2 on spleen cells, when activated by THC, suppress the system whereby a secondary messenger substance is released in the cells. This results in the suppressed system reducing the functioning of the spleen cells involved in the immune response.

Laboratory experiments exposing human and rodent cells to THC or other marijuana ingredients resulted in the inhibition of the normal disease-preventing reactions of many key types of immune cells (Adams and Martin 1996).

T-cell proliferation was found to be normal in a group of marijuana smokers but when examined more closely there was an increase in one sub-set and a decrease in another (Wallace et al 1988, Whitfield et al 1997). Intermittent disturbances in T and B cell function were found but the magnitude was small and other measures were frequently normal (Klein et al 1998).

Professor Guy Cabral of The Department of Microbiology and Immunology, Virginia Commonwealth University, in the last 20 years has written over 50 papers on the subject of marijuana and the immune system.

In 1998 Cabral and Pettit wrote a review paper on the subject of cannabis and immunity. "This substance *(THC)* has been shown to be immunosuppressive and to decrease host resistance to bacteria, protozoan and viral infections. Macrophages, T-lymphocytes and natural killer cells appear to be major targets of the immunosuppressive effects of THC. Definitive data which directly links marijuana use to increased susceptibility to infection in humans is currently unavailable, however the fact that current literature reports indicate that THC alters resistance to infection in vitro in a variety of experiments on animals supports the hypothesis that a similar effect occurs in humans.

Cabral wrote another review of the literature in 1999 in *Marijuana and Medicine* (Nahas and Latour eds). "Marijuana has been shown to decrease host resistance to bacterial, protozoan and viral infections in experimental animal models and in vitro systems. Recent immuno-epidemiological studies suggest that marijuana may also influence the outcome of viral infections in humans……Delta-9-THC alters the functioning of an array of immune cells including lymphocytes, natural killer cells and macrophages, thereby affecting their capacity to exert anti-microbial activities….At sites such as the lung… THC may alter cellular membranes because of its highly lipophilic nature…, at sites distal to the lung, THC, at relatively low concentrations may exert its suppressive effects on immune cells by interacting with cannabinoid receptors CB1 and CB2".

A Columbia study in 1999 by Dr James Dobson found a control group smoking a single marijuana cigarette every other day for a year had a white blood cell count 39% below the normal. He said, " Marijuana can cause great harm".

Apoptosis is the key mechanism programmed by the genetic code which regulates the life and death of a cell. It is the "programmed cell death" of all mammalian cells. Apoptosis relates to the destruction of the DNA formation by the cell itself. Professor Gabriel Nahas, interviewed for an Italian newspaper, Italy Daily Roma in 2000 said the process accounted for the findings more than twenty-five years (1973) before of the damaging effects of marijuana and THC on lymphocytes. THC induces apoptosis of the cells. Because of the long-term storage of THC in body fat, the "death signals" from the THC remain in the body and act on the cells for weeks.

Cultures of immune cells from mice, splenocytes and peritoneal macrophages were treated with THC and the DNA fragmentation preceded membrane damage, indicating that THC induced apoptosis rather than necrosis (Zhu et al 1998).

Mice exposed to THC or related substances were more likely to develop bacterial infections and tumours than unexposed mice (Zhu et al 2000).

Friedman and his colleagues produced a review paper in 2003. It covered several drugs of abuse and their effects on immunomodulation. He said, "Recent studies of the effects of opiates or marijuana on the immune system have demonstrated that they are receptor mediated, occurring both directly via specific receptors on immune cells and indirectly through similar receptors on cells of the nervous system.

Another deleterious effect of cannabis on the immune system was found by Tohyama and others in 2006. Cannabis can cause some white blood cells to lose the ability to migrate to sites of infection and inflammation. The cells seemed to lose their ability to develop a front/rear polarity needed to migrate to these sites.

The immune system has a part to play in the development of cancer through the activity of alveolar macrophages. The following paragraph is also included in my section on cannabis and cancer.

Alveolar macrophages protect the lungs from infection, they also kill tumour cells. Marijuana and tobacco smokers produce two or three times as many of these cells as non-smokers. The effects of smoking both being additive (Barbers et al 1987). The macrophages in both tobacco and marijuana smokers were larger and had more inclusions, probably due to the ingestion of smoke particles (Beals et al 1989). A more recent paper by Baldwin and others in 1997 found significant impairment of the macrophage cells of both tobacco and marijuana smokers. These cells have been shown to have cannabis receptors (Bouaboula et al 1993). Anti-tumour immunity depends on antigen-presenting dendritic cells being able to stimulate the proliferation of T lymphocytes that identify and destroy tumour cells. The in-vitro studies in which dendritic cells and T lymphocytes were incubated with or without THC, the THC suppressed the T cell proliferation in a dose-dependent manner (Roth et al 1997). Two earlier papers were written on this subject in 1975 by Petersen et al and Nahas et al.
DNA alterations have been seen in the lymphocytes of pregnant marijuana smokers and their newborns. This study is particularly important as tobacco smokers were excluded (Ammenheuser et al 1998). Cannabis smoking also depressed pro-inflammatory cytokine production. Cytokines regulate macrophage function so this may account for the impairment of their ability to kill tumour cells (Baldwin et al 1997).

Low levels of THC inhibited the tumour necrosis factor, thereby weakening the killing activity of lymphocytes against tumour cells (Kusher et al 1994).

Zhu and colleagues in 2000 showed that THC suppresses host immune reactivity against lung cancer. In two different lung cancer models in mice, intermittent administration of THC led to accelerated growth of tumour implants. He said, "Our findings suggest that THC promotes tumour growth by inhibiting anti-tumour immunity by a CB2 receptor-mediated pathway".

Pacifici and others in 2003 found cannabis smokers had fewer natural immune-enhancing killer cells and lymphocytes and higher levels of a protein that may promote tumour growth called interleukin-10. These changes can dampen the immune system's responses to infection, increasing susceptibility to infection and promoting tumour growth.

"The inability of alveolar macrophages from habitual marijuana smokers without apparent disease to destroy fungus, bacteria and tumour cells, and to release pro-inflammatory cytokines, suggests that marijuana might be an immunosuppressant with clinically significant effects on host defence. Therefore the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with

pre-existing immune deficits – including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients)" (National Academy of Sciences *Marijuana and Medicine* 1999).

There have been a few papers putting forward the idea that cannabinoids or their metabolites may prove useful in the treatment of some cancers.

The administration of THC and a synthetic cannabinoid agonist into the tumour induced a considerable regression of malignant gliomas in rats and in mice. No substantial neurotoxic effect was produced by the cannabinoid treatment in the conditions employed.
Two glioma cell lines in culture demonstrated that the cannabinoids signalled apoptosis in the cells. It was suggested that these results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas (Galve-Roperph et al 2000).

A metabolite of THC is 11-COOH-THC, and ajulemic acid (AJA) is a synthetic analogue of it. In cell cultures AJA proved to be approximately one half as potent as THC in inhibiting tumour growth against a variety of tumour cell lines. However its effects lasted longer. The conclusion was that AJA produced significant anti-tumour activity and effected its actions primarily through CB2 receptors (Recht et al 2001).

Casanova and colleagues in 2001 showed that both CB1 and CB2 receptors are present in hair follicles and skin. The synthetic cannabinoid WIN55, 212-2 induced a decrease in the viability of several mouse skin cancer cell lines, non-cancer lines being unaffected. This occurred through the process of apoptosis. CB1 and CB2 receptors were involved.

Providing that purified single extracts of cannabinoids or synthetic equivalents are subjected to the rigorous clinical testing required by law, there should be no objection to these proposals. Crude cannabis is not a candidate for medical use.

Zhang et al in 2007 produced a paper showing that "the use of cannabinoids may place individuals at greater risk of the development and progression of Kaposi's sarcoma. The herpesvirus associated with the development of Kaposi's sarcoma, KSHV, is needed but insufficient for its development. Marijuana was investigated for its effect on this disease. "Our results indicate that delta 9 THC can enhance KSHV infection and replication and foster KSHV-mediated endothelium transformation. Thus, use of cannabinoids may place individuals at greater risk for the development and progression of Kaposi's sarcoma".

Cannabis has been shown to modulate mitochondrial function and induce cell death in a paper in 2007 by Athanasiou and others. Time-lapse microscopy of human lung cancer (H460) cells showed that anandamide (AEA), THC and a synthetic cannabinoid (HU210) all caused morphological changes characteristic of apoptosis. All 3 ligands caused significant decreases in oxygen consumption and mitochondrial membrane potential in rat heart mitochondria. THC and HU210 significantly increased the production of hydrogen peroxide, AEA had no significant effect. Further evidence was obtainedof the damaging effects on mitochondria (the structures in cells which produce energy).

In 2007 a paper by Eisenstein et al found that both THC and anandamide directly inhibit cells of the immune system via CB2 receptors.

A paper by Chao et al in 2008 found that recreational drug use does not adversely affect CD4 cell counts. They wrote, "We did not find any clinically meaningful associations, adverse or otherwise, between use of marijuana, cocaine, poppers, or amphetamines and T-cell counts and percentages in either HIV-uninfected or HIV-infected men". However in their conclusion they added, "although the circulating numbers of CD4 and CD8 T cells do not appear to be significamntly affectedby use of these substances, these findings do not preclude the possibility that substance use may adversely affect the functional properties of T cells".

Ishida and others in January 2008 found that chronic marijuana use may increase fibrosis for Hepatitis C patients. Between 2001 and 2004, 204 patients with hepatitis C were interviewed for risk factors associated with HCV and use of alcohol and cannabis. Virologic testing and liver biopsies were carried out. Current daily cannabis use increased the odds of moderate to severe fibrosis by nearly 7-fold. This study confirms an earlier French one of 2004 which came to the same conclusion of an increase in fibrosis in daily users.

A paper in February 2008 (Thomson et al) found that cannabis smoking may be a risk factor for periodontal disease, independent of tobacco use. The Dunedin NZ Longitudinal Study supplied the data fror this research. Three groups were determined, no exposure to cannabis, 293(32.3%), some exposure, 428(47.4%) and high exposure, 182(20.2%) .The incidence of Combined Attachment Loss (CAL), between 26 and 32 years of age, in the none group was 6.5%, s ome exposure 11.2% and high exposure 23.6%. After conrolling for tobacco use, sex, irregular use of dental services and dental plaque, the relative risk estimates of the highest group were 1.6 for having 1 or more sites with 4mm or greater with CAL, 3.1 for having 1 or more sites with 5mm or greater CAL and 2.2 for having CAL compared with the "none" group.

Hegde et al, 2010 found that THC suppresses the immune system by massively expanding the number of myeloid-derived suppressor cells (MDSC) both in vivo and in vitro. These cells in the immune system have only recently been discovered. These cells have been known to increase in cancer patients so they may suppress the immune system against cancer chemotherapy, actually promoting cancer growth . The lead author, Dr Prakash Nagarkatti concluded, 'Marijuana cannabinoids present us with a double-edged sword. On one habnd due to their immuno-suppressive nature, they can cause increased susceptibility to cancer and infections. However, further research of these compounds could provide opportunities to treat a large number of clinical disorders where suppressing the immune system is actually beneficial'.

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Cannabis, Depression, Aggression, Violence and Suicide

The association between cannabis use and depression has received much less attention than that between cannabis use and psychosis. It may be that depressed people are less likely to seek treatment than those with psychosis (Degenhardt et al, 2001).

Thomas reported in a review article in 1993, that it was not possible to find scientific proof that cannabis causes a depression of clinical proportions. However he said there was a large body of clinical observations showing that short-lived dysphoric episodes can be provoked by the use of cannabis.

In Andreasson and Allbeck's study of 45,000 Swedish conscripts (1990) exploring relationships between cannabis, schizophrenia and suicide, they concluded that the cannabis indirectly increases the risk of suicide as a result of its ability to precipitate, exacerbate and cause depression and psychosis. In other words, the increasing frequency of suicides in large scale users was thought to reflect the increased frequency of depression in cannabis abusers.

Weller (1989) compared cannabis abusers, users and non-users in outpatients. Fifty-five per cent of the abusers had clinical depression according to the DSM III. Rowe (1995) found an association with marijuana and depression in women. However both these studies have many confounding factors known to be responsible for causing depression e.g. use of alcohol and sedatives, family background with significantly higher levels of drug abuse, criminal activity and suicide. So a causal connection was impossible to establish.

Data from The US National longitudinal Alcohol Epidemiologic Survey indicated a diagnosis of cannabis use or dependency in the last year was associated with a 6.4 fold increased chance of receiving a diagnosis for major depression in that time (Grant 1995).

Green and Ritter in 2000, in a large drug use survey of men born between 1944 and 1954 found that marijuana users who use the drug to cope with problems are more depressed than those who do not use it to cope with problems.

More recently though, the questions of whether cannabis is a risk factor for causing depression, or depressed people use cannabis to self-medicate has been tackled by Bovasso in 2001. Based on data from 1980, he examined 1920 people in 1995.
"In participants with no baseline depressive symptoms, those with a diagnosis of cannabis abuse at baseline were four times more likely than those with no cannabis abuse diagnosis to have depressive symptoms at the follow-up assessment, after adjusting for age, gender, antisocial symptoms, and other baseline covariates. These symptoms mostly took the form of suicidal thoughts. Among the participants who had no diagnosis of cannabis abuse at baseline, depressive symptoms at baseline failed to significantly predict cannabis abuse at the follow-up assessment". This last finding was also reported by Kandel et al in 1984 and in 2000 by Kandel et al and McGee et al. In 2005, Hallfors et al also concluded that "Engaging in sex and drug behaviours places adolescents, and especially girls, at risk for future depression".

JS Brook and others in 2001 published a longitudinal study on over 2000 Colombian adolescents. A clear connection was found between marijuana use and raised levels of anxiety and depression. A prediction can be made of later distress in adolescence if marijuana is used at an early age.

DW Brook and others in 2002 in another longitudinal study found that early marijuana use in childhood and adolescence increased the risk of major depression by 17%. Again the warnings were given of the implications for psychiatric problems later in life because of early use.

Patton and others (2002) followed the progress of 1600 young people, male and female from the age of 14/15 in 1997/8, starting by and large before they had any mental problems or had used drugs. He studied them at 14/15 and again at 21/22. Daily use of cannabis in young women but not men, was linked with an increased risk of between 4 and 5 times in the odds of reporting a state of depression after adjustment for co-founding factors. Weekly use was associated with around a twofold greater risk for depression and the prevalence of the condition increased with higher usage of the drug. They also showed that depression in teenagers did not give rise to an increased cannabis use in early adulthood.

Chen and others (2002) on re-analysing the US National Co-morbidity Survey (NCS), found that those dependent on cannabis at some time in their lives was associated with a 3.4 times greater risk of major depression. And also in 2002 in Australian adolescents a moderate connection was discovered between cannabis use and depression after taking account of other drug use, age and gender. The correlation was most marked in those who had used once or more in the last month (Rey et al, 2002).

2002, Vlahov D et al found that New Yorkers who increased their use of marijuana , tobacco or alcohol after September 11th had increased chances of developing Post Traumatic Symptoms. Marijuana increased both PTS symptoms and depression more than the other substances.

Degenhardt et al (2003) reviewed the literature on this subject and produced the following results. "There was a modest association between heavy or problematic cannabis use and depression in cohort studies and well-designed cross-sectional studies in the general population. Little evidence was found for an association between depression and infrequent cannabis use. A number of studies found a modest association between early-onset, regular cannabis use and later depression, which persisted after controlling for potential confounding variables. There was little evidence of an increased risk of later cannabis use among people with depression and hence little support for the self-medication hypothesis. There have been a limited number of studies that have controlled for potential confounding variables in the association between heavy cannabis use and depression. These have found that the risk is much reduced by statistical control but a modest relationship remains".

Another review was conducted in 2004 by Rey and others. Their results were very similar. "There is growing evidence that early and regular marijuana use is associated with later increases in depression, suicidal behaviour and psychotic illness, and may bring forward the onset of schizophrenia. Most of the recent data reject the view that marijuana is used to self-medicate psychotic or depressive symptoms".

In a study of 600 same-sex twins, only one of whom was cannabis dependent, it was found that the risk of major depressive disorder was greater in the cannabis dependent twin of fraternal twins; this was not borne out in identical twins (Lynskey et al, 2004).

Other papers indicating a significant association between cannabis use and depressive orders include: Kelder et al (2000), Winokur et al (1998), Troisi et al (1998) and Miller et al (1996).

It is very difficult to determine whether cannabis is associated with violence due to the use of cannabis, withdrawal from the drug, a personality predisposition to violence or indeed because of the illegality. Disputes often arise between drug dealers, users and peers (Arsenault et al 2000). Professor Heather Ashton says in her 1999 review article, 'Adverse effects of cannabis and cannabinoids' that "cannabis in most recreational settings decreases aggressive feelings in humans and increases sociability. However, occasional predisposed individuals, especially if under stress, become aggressive after taking cannabis. Violent behaviour may also be associated with acute paranoid or manic psychosis induced by cannabis intoxication".

Dyer (1996) wrote in the BMJ that, "Drug or alcohol misuse combined with a mental disorder could treble or quadruple the risk of violence".

Two studies by Kouri and others (1999 and 2002) investigated aggression during withdrawal from cannabis. The Harvard Study in 1999 compared 17 long-term heavy users with 20 infrequent or former smokers. All abstained from the use of cannabis and all other drugs for the duration of the experiment. They were not told that they were being monitored for aggression - temperature and heart rates were measured, so data were not gathered by "self-reporting". The heavy users showed much more aggression than the controls especially in the first week of abstinence. By day 28 this behaviour had faded.

In the 2002 study they monitored 30 current users and 30 controls (16 former heavy users and 14 light users). There was no difference between the groups to start with except in the ability to concentrate which was worse in the current users. The subjects reported an increase in irritability, anxiety, tension and physical symptoms peaking 7 to 10 days after abstinence. Thus from the 2 studies it can be argued that "aggressive responses of current cannabis users are due to marijuana withdrawal rather than a mere history of marijuana use".

2001 Friedman et al investigated violent behaviour as related to use of marijuana and other drugs. A sample (number 612) of African-American inner city young adults was studied. Unexpectedly, greater

frequency of marijuana use was found to be associated with greater likelihood to commit weapons offences. This association was not found with any other drug except alcohol. There was also an association between marijuana and attempted homicide/reckless endangerment offences.

Fergusson and others during The Christchurch Cohort Study in 1997 when the subjects were aged 16, assessed them for cannabis and violence (assault, fighting, weapon use, threats of violence against another). There was a dose-response relationship with higher cannabis use and an increasing number of violent offences which persisted after controlling for other drug use and peer criminal behaviour, suggesting that deviant peer affiliations are not responsible. In a follow-up at the age of 21 (2002), they found the same association. The link was especially strong in those who had started using early, between 14 and 15 and were regular users (weekly or monthly). An increased frequency in incidents of property or violent crime, depression, suicidal ideation and suicide attempts was observed. The authors pointed out that there was a possibility that pre-existing psychosocial problems may have encouraged cannabis use rather than the other way around so caution must be applied and the results may not indicate a causal explanation for cannabis.

Spunt et al (1994) interviewed 268 people in prison for murder in New York State in 1984. 73 had been under the influence of cannabis at the time and 18 said that the use of cannabis was linked to their crime. When asked, 4 of them said it made them violent and aggressive, one said that when he was high he lost control and another that he doubted he would have done it had he not been under its influence. Four were of the opinion that it lowered their inhibitions and 2 said it made them paranoid. Some who were under the influence of both cannabis and alcohol at the time said the combined effect made them lose self-control.

Twelve cases of aggravated violent crime were looked at in Geneva between 1996 and 2000 (Niveau and Dang, 2003). All the perpetrators were under the influence of only cannabis at the time. Others were discarded because of poly-drug use. Five were previously known to have a personality disorder and three others had psychiatric disorders. All twelve suffered from severe negative effects of cannabis use. Four had an acute psychotic condition, one a relapse into or exacerbation of chronic paranoid psychosis, another 3 had intense anxiety and 3 delirium. The remaining one had a “mood” disorder. There is a growing interest in “dual diagnosis”, ie cannabis use is included as one of the disorders. There is also growing concern about the combination of alcohol and cannabis.

Serious problems of fighting with weapons, window breaking and theft in males and aggressive acts, violent quarrels with teachers, openly cursing or being sent to see the school head in females were all predictors for early cannabis initiation (Pederson et al 2001). Hall JA and others (2003) said that users of cannabis at an early age are at greatest risk of delinquency and violence. They are also most likely to engage in such behaviours before beginning to use cannabis.

Arsenault and others in their “Dunedin Study 2000”, discovered that alcohol dependent individuals were almost twice, marijuana-dependents almost 4 times, and those suffering from schizophrenia spectrum disorder, two and a half times more likely than controls to be violent (Arsenault et al, 2002).

Friedman et al in 2003 found that, for a conventional non-delinquent sub-group, a higher degree of significant relationship between degree of marijuana use and degree of violence occurred, compared to the degree of this type of relationship than was found for either cocaine/crack use , amphetamine use, or tranquilliser/sedative use. In a group that is high on delinquent behaviour, the effect of marijuana was less. Thus, this special disinhibiton effect was found only for marijuana and not for the other drugs.

A more recent investigation among 5,500 Dutch adolescents between 12 and 16, found that criminality and aggression increased with increasing use of cannabis. No link was discovered between internalising problems, withdrawal and behaviour. Social factors, regular tobacco smoking and alcohol use were all taken into account. Significant associations were only found in those who had used the drug recently (Monshouwer, 2006)

A series of surveys by PRIDE (Parent Resources and Information on Drug Education USA) and ONDCP (Office of National Drug Control Policies) in 2006 added more evidence of the link between cannabis use and violence.
Of those students who reported carrying a gun to school during the 2005/6 school year, 63.9% had also used marijuana, 39.9% cocaine and 36.8% crystal meth in the past year. (PRIDE Surveys (2006) Questionnaire report for grades 6-12: 2006 National Summary 184).
Of those students who reported hurting others with a weapon at school, 68.4% had used marijuana, 48.3% cocaine and 44.1% crystal meth in the past year. (PRIDE surveys 2006 etc 197)

The incidences of youth physically attacking others, stealing, and destroying property increased in proportion to the number of days marijuana was smoked in the past year. Marijuana users were twice as likely as non-users to report they disobeyed school rules. (Office of National Drug Control Policy 2006 *Marijuana Myths and Facts: The Truth Behind 10 Popular Misperceptions 10).*
Of those students who reported threatening someone with a knife, gun or club, or threatening to hit, slap or kick someone in the school year 2005/6, 27% had used marijuana, 7.8% cocaine and 6.2% crystal meth in the past year (PRIDE surveys (2006) etc 194).
During the school year 2005/6, 39.6% of those in trouble with the police used marijuana, 12.2% cocaine and 9% crystal meth in the past year (PRIDE surveys (2006) etc 195).
PRIDE surveys are available: http://www.pridesurveys.com/customercenter/us05ns.pdf.

In a Welsh study of 740 identical and non-identical twins, it was found that, while the environment played a part in the development of cannabis use disorder in those with conduct disorder, genetics had a significant influence. Therefore the absence/presence of a conduct disorder in a twin pair is a good predictor of cannabis use. The findings suggest that cannabis use and violence to some extent co-occur due to personality tendencies (Miles et al, 2002).

Other researchers to find a connection between cannabis and violent behaviour are: Resnick et al, 1997, Dornbusch et al, 1999, Friedman, 1996 and White, 1998.

A 1995 (Fugelstad et al) Swedish study looked at suicides. In a study of 53 people who jumped from a great height, 11% were under the influence of cannabis, a disproportionate number. They calculated that a cannabis smoker is 18.7 times more likely to take his own life by jumping than a non-smoker. The number of cannabis-related suicides, in comparison with suicides related to the use of other drugs, users of heroin, amphetamines or alcohol, was much higher and none of them jumped from high places or committed murder before taking their own lives. No homicides were carried out by the users of other drugs who committed suicide.

Beautrais et al (1999) found only a very limited independent association between cannabis and suicide but indicated the indirect link by way of psychosis and depression, both of which can increase suicide rates.

The Australian News on November 25th 2002 reported a "Marijuana suicide epidemic" among the Aborigines in The Northern territories. In one community of 650 people, 30 suicide attempts related to cannabis were made in one year , in one month period, 3 succeeded. It appeared that they were buying marijuana, mixing it with alcohol and becoming paranoid.

Research was carried out in the Caribbean island of Trinidad where there is an established use of cannabis and high suicide rates. "Depression and psychotic experiences were common findings in adolescent cannabis users with a significant preponderance of depressive experiences. Our findings suggest that there is a convincing relationship between suicidal behaviour and cannabis use"(Maharajh and Konings, 2005).

Heavy cannabis use and depression were linked in a study on 3 Aboriginal communities in Arnhem Land in the Northern Territory in May 2008 by Lee and others. "After adjusting for other substance use (tobacco, alcohol and lifetime petrol sniffing) age and sex, heavy cannabis users were 4 times more likely than the remainder of the sample (106 individuals0 to report severe depressive symptoms".

There have been numerous reports in the press linking cannabis with violent incidents and suicide. These are a few examples:

A wealthy 52 year-old music producer was attacked in her home by a 20 year-old family friend made psychotic by the drug. She had to have 11 operations to rebuild her face. At the time doctors warned she would likely die (The Times 5/02/06). A judge attacked the use of cannabis after a 25 year-old professional golfer with a history of cannabis smoking killed his grandmother and aunt in a frenzied attack (Daily Mail 25/11/03). A coroner blamed cannabis for 2 deaths after a long-running feud over a hedge. A 52 year-old man grew his own supplies in his attic and had become addicted after smoking between 5 and 10 cannabis cigarettes a day. He shot his 66 year-old neighbour then committed suicide a week later in prison (Daily Mail 16/01/04). A teenager stabbed himself to death in the chest with scissors in front of his helpless father, he thought he was invincible. He had previously threatened his sister and girlfriend (Daily Mail 28/02/02). Then there was the well-publicised case of Luke Mitchell, 16 who slashed and killed his 14 year-old girl friend Jodi Jones in Scotland. He told his psychiatrist he smoked 600 joints a week (Daily Mail 12/02/05).

Britain's most senior coroner, Hamish Turner, issued warnings in various papers in November 2003 that hundreds of young people are dying because of prolonged use of cannabis. He claimed that, over the last year , of the 100 deaths he had dealt with, 10% had a significant link to the drug (Daily Mail 3/11/03).

A 22 year-old nurse smoked cannabis for 5 years, became very depressed and hung himself in his bedroom (Daily Mail 12/06/05). A student hung himself after developing a mental illness induced by the use of cannabis. He left a suicide note which read, "Cannabis has ruined my life" (The Times 9/09/03). James Taylor hanged himself in his Torquay flat after smoking cannabis since he was 15. He suffered mental health problems and depression (Daily Mail 3/11/03).

I recently met a nurse from a GP Practice. She said, "If only people could come in and look at the records. The number of our young patients they would see who have as their priority condition: "Marijuana-induced depression, Marijuana-induced psychosis or Marijuana-induced schizophrenia, would really bring the problem home to them. They would not believe it. This is a huge problem".

"Teens Drugs and Violence", a special report from the Office of National Drug Control Policy in the USA, in June 2007 concluded that "Early use of marijuana – the drug most widely used by teens – is a warning sign for later gang involvement" and " Teens who participate in gangs are more likely to be involved in violent acts and drug use". "Teens who report current and regular marijuana use are 9 times more likely than non-users to experiment with other illegal drugs or alcohol, and five times more likely to steal….Children who use marijuana are nearly four times more likely to join gangs. Being a member of a gang dramatically increases a teen's risk of being a victim of violence, not just a perpetrator".

A possible mechanism for cannabis-induced violence was found in a paper by Howard and Menkes in October 2007. Five habitual cannabis users were given a reefer containing 11mg of THC. An electrocortical measure of affective impulsivity, Go/No Go contingent negative variation was carried out during and after smoking. Slow brain potentials developed normally in both Go/No Go conditions before and during smoking but were severely disrupted 20 to 30 minutes later – peak intoxication! (The effects were said to resemble those occurring in patients with lateral prefrontal cortex lesions). Larger scale studies were called for.

In 2009 Dr Gabriella Gobbi found that teenage cannabis users have decreased serotonin transmission leading to mood disorders, and increased norepinephrine transmission which leads to greater long-term susceptibility to stress. She Said, " Our study is one of the first to focus on the neurobiological mechanisms at the root of this influence of cannabis on depression and anxiety in adolescents." It is also the first to demonstrate that cannabis causes more serious damage during adolescence than adulthood.

2010 Fazel and others conducted a study into bipolar disorder and violent crime. Participants were: individuals with 2 or more discharge diagmnoses of bipolar disorder (n =3743), general population controls (n = 37,429) and unaffected full siblings of individuals with bipolar disorder (n = 4059)
314 individuals with bipolar disorder (8.4%) committed violent crime compared to 1312 general poulation controls (3.5%). The risk was mostly confined to patients with substance abuse co-morbidity, and minimal in patients without without substance use comorbidity. This was further attenuated when the unaffected full siblings were used as controls. They concluded, ' Although current guidelines for the management of individuals with bipolar disorder do not recommend routine risk assessment for violence, this assertion may have to be reviewed in patients with comorbid substance abuse'.

2011 Otten et al found that cannabis smoking increases the risk of depression in the case of genetic vulnerability. Data were collected over 5 years from 428 families and their 2 adolescent children in Holland. In young people with a variant of the gene 5-HTT cannabis use led to an increase in depressive symptoms. The effect was still'robust' even accounting for alcohol use, smoking, upbringing, socio-economic staus or personality.

Daily Mail Tuesday September 28th 2010 reported the case of a public schoolboy, hooked on cannabis, who stabbed his best friend 13 times and left him for dead. Harry Schick, 17, was locked up for 9 years. The boy, Gavin Doyle, was able to dial 999 and was rescued from woods by a helicopter with heat-seeking equipment. He is still experiencing problems from wounds to his hands. "Schick had no history of violence though his psychiatric report said that his heavy use of cannabis had led him to become distanced from reality".

2010 de Graaf et al looked at early cannabis use and depression. They concluded: The overall association was modest (controlled for sex and age), was statistically robust in 5 countries, and showed no sex difference. The association did not change appreciably with statistical adjustment for mental health problems, except for childhood conduct problems, which reduced the association to nonsignificance. This study did not allow differentiation of levels of cannabis use; this issue deserves consideration in future research.

2012 August Fergusson et al looked at The Christchurch Health and Development Study (1265 NZ children born in 1977 and studied at 4 months, 1 year, then yearly till age of 16, then at 18, 21, 25 and 30). These research findings were presented at The Second national Cannabis Conference in Brisbane on September 20th 2012. Not only did cannabis use precipitate suicidal thoughts but the higher the frequency of regular use, the faster susceptible individuals became suicidal. If all males used cannabis less frequently than several times/week, suicidal ideation would be experienced by 15% of 18 year olds, 24% of 21 year olds and 30% of 30m year olds. If they had all started using cannabis several times a week from the age of 17, then all males would show an increase of 24% of 18s and 31% for 21s.

2012 November Sheehan and others looked at gender differences in the presence of drugs in violent deaths. Conclusions: Suicide and homicide decedents are characrterized by varying patterns of licit and illicit drug use that differ by gender. Drugs associated with homicides (marijuana, cocaine and amphetamines) are stronger among males, while drugs associated with suicide are stronger among females (antidepressants and opiates). Taking these differences into consideration may allow for targeted interventions to reduce violent deaths.

2012 Reingle et al looked at the relationship between marijuana use and intimate partner violence. Abstract: Intimate partner violence is a significant public health problem, as these behaviors have been associated with a number of negative health outcomes including illicit drug use, physical injury, chronic pain, sexually transmitted diseases, depression, and posttraumatic stress disorder. The current study examined the association between marijuana use and intimate partner violence using a longitudinal survey of adolescents and young adults ages 15 to 26 years. Data were obtained from 9,421 adolescents in the National Longitudinal Study of Adolescent Health (Add Health) Waves 1 through 4 (1995-2008). Marijuana use was measured in the past year at each wave and participants were categorized as "users" or "nonusers." Partner violence was constructed using six items (three pertaining to victimization and three concerning perpetration) from Wave 4 (2007-2008). Using these six items, participants were categorized as "victims only," "perpetrators only," or "victims and perpetrators." Survey multinomial regression was used to examine the relationship between marijuana use and intimate partner violence. Consistent use of marijuana during adolescence was most predictive of intimate partner violence ($OR = 2.08$, $p < .001$). Consistent marijuana use ($OR = 1.85$, $p < .05$) was related to an increased risk of intimate partner violence perpetration. Adolescent marijuana use, particularly consistent use throughout adolescence, is associated with perpetration or both perpetration of and victimization by intimate partner violence in early adulthood. These findings have implications for intimate partner violence prevention efforts, as marijuana use should be considered as a target of early intimate partner violence intervention and treatment programming.

2013 Smith et al reported that laboratory-based increases in aggression due to marijuana withdrawal extend to the general population of marijuana users who have a previous history of aggression.

2013 Wong and others looked at clinical implications of substance use on suicidality among youths. Data from The Youth Risk Behaviour Survey from 2001 to 2009 were used to analyse the correlation between lifetime use of 10 common substances of abuse – heroin, alcohol, cocaine, ecstasy, hallucinogens, methamphetamines, steroids, tobacco, inhalants, marijuana. The study controlled for multiple co-founders. The key findings concluded that a history of all substance abuse is a strong and independent risk factor for adolescent suicide ideation, and plans, and attempts – even after controlling for eg depression, eating disorders, interpersonal violence etc. 4.1% of adolescents who reported at least once /lifetime marijuana use made a suicide attempt that required medical attention compared with 0.89% who reported never using marijuana. The greater the number of substances used, the more attempts were made.

2013 Brook et al looked at the relationship of marijuana use from adolescence to adulthood and the use of weapons including guns. African Americans and Puerto Ricans (838). There was a higher probability of engagement in violence (shooting or hitting with a weapon) among those with increasing marijuana use, moderate use and the quitter group than those with no use.

2014 SAMHSA (Substance Abuse and Mental Health Services Administration) in the USA 2012 Survey of Drug Use and Health (70,000 individuals age 12 or over) found that adults using illicit drugs are

significantly more likely to contemplate suicide than the general adult population. 3.9% of US adults in a given year (9m) have serious thoughts of suicide . This rises to 9.4% of those who use illicit drugs. This varied with the type of drug used. Sedatives produced a 21% rise, opioid pain relievers 13% and marijuana 10%.

2014 Zang and Wu found that ideation of suicide and substance abuse among adolescents and young people increased the risk of illicit drug use. 3342 people were tested on 4 occasions from 1995 to 2009. Their conclusion, 'Use of cigarette or alcohol increased risk of suicidal ideation, while suicidal ideation was not associated with cigarette or alcohol use. Reversely, drug use (marijuana and other drugs) did not increase risk of suicidal ideation, but suicidal ideation increased risk of illicit drug use'.

2014 Cairns et al studied risk and protective factors for depression in a systematic review and meta-analysis. 113 publications were identified (longitudinal studies of 12-18 year olds) which met the criteria. They concluded that future health education campaigns should aim to reduce substance abuse (alcohol, tobacco, cannabis, other illicit drugs, and polydrug use); dieting; other negative coping strategies; and to promote heathy weight; diet and sleep patterns.

2015 Jan. Ansell et al found hostility and impulsivity among marijuana users in daily life. Forty three participants with no substance dependence reported on their alcohol consumption, tobacco use, recreational marijuana use, impulsivity, and interpersonal hostility in others over 14 days.
Marijuana use was associated with increased impulsivity on the same day and the following day relative to days when marijuana was not used, independent of alcohol use. Marijuana was also associated with increased hostile behaviors and perceptions of hostility in others on the same day when compared to days when marijuana was not used. These effects were independent of frequency of marijuana use or alcohol use. There were no significant effects of alcohol consumption on impulsivity or interpersonal hostility.
CONCLUSIONS: Marijuana use is associated with changes in impulse control and hostility in daily life. This may be one route by which deleterious effects of marijuana are observed for mental health and psychosocial functioning. Given the increasing prevalence of recreational marijuana use and the potential legalization in some states, further research on the potential consequences of marijuana use in young adults' day-to-day life is warranted**.**

2015 Moitra et al investigated depression in female emerging adults. 332 emerging female adults (18-25 years) were studied for changes in depressive symptoms in relation to changes in cannabis use at 3 months and 6 months. Changes were significantly stronger for those with mild and moderate and more severe depression relative to those with minimal depression. Reduction in depression correlates with reduction in cannabis use.

2015 Kylie et al looked at cannabis use and violence among 3 Aboriginal Australian communities. 264 random individuals between 14 and 42 were selected. Physical trauma presentations between June 2004 and June 2006 were used. One in 3 of them (88) presented with physical trauma. The majority (58) had at least one presentation that was violence-related. Nearly 2 in 3 of the total presentations for trauma following violence involved the use of a weapon, hunting tools, wooden or rock implements. Individuals who reported any current cannabis use were nearly 4 times more likely than non-users to present at least once for violent trauma, after adjusting for alcohol, age and sex.

2015 Pardini et al examined the linkages with criminal behaviour and psychopathic features of males into the Mid 30s. Chronic high and late-increasing marijuana users exhibited more adult psychopathic features and were more likely to engage in drug-related offending in the mid-30s than low/non-users. Adolescence-limited users were similar to non/low users in terms of psychopathic features but more likely to be arrested for drug-related crime.

2015 Wilkinson et al looked at marijuana use in patients with PTSD. They found, after relevant baseline co-variants that marihuana use was significantly associated with worse outcomes in PTSD symptom severity, violent behaviour, and measures of drug and alcohol abuse, compared to those who stopped (used at admission but not after discharge) and never-users. Those two groups also had the lowest levels of PSTD symptoms at follow-up, while starters (used after discharge but not at admission) had the highest levels of violent behaviour.

2016 Schoeler et al looked at continuity of cannabis use and violent offending over the life course. The study (The Cambridge Study in Delinquent Development) involved 411 boys all born around 1953, raised in working class urban areas in London, 97% were Caucasian and all were raised in 2-parent households.

Researchers controlled for a number of factors, including antisocial traits e.g. alcohol or other drug use, cigarette smoking, mental illnesses and family history etc. Most of the participants never used cannabis and they were never reported to have violent behavior. 38% of the participants did try cannabis at least once in their life. Most of them experimented with cannabis in their teens, but then stopped using it. However, 20% of the boys who started using pot by age 18 continued to use it through middle age (32-48 years). One fifth of those who were pot smokers (22%) reported violent behavior that began after beginning to use cannabis, whereas only 0.3% reported violence before using weed. Continued use of cannabis over the life-time of the study was the strongest predictor of violent convictions, even when the other factors that contribute to violent behavior were considered in the statistical analysis. In conclusion, the results show that continued cannabis use is associated with a 7-fold greater odds for subsequent commission of violent crimes. This level of risk is similar to the increased risk of lung cancer from smoking cigarettes over a similar duration (40 years). The authors suggest that impairments in neurological circuits controlling behavior may underlie impulsive, violent behavior, as a result of cannabis altering the normal neural functioning in the ventro-lateral prefrontal cortex.

2016 Rodway et al looked at suicides in young people.

Findings: '145 suicides in people younger than 20 years were notified to us during the study period (January 1st 2014 – April 30th 2015), of which we were able to obtain report data about antecedents for 130 (90%). The number of suicides rose sharply during the late teens with 79 deaths by suicide in people aged 18–19 years compared with 66 in people younger than 18 years. 102 (70%) deaths were in males. 92 (63%) deaths were by hanging. Various antecedents were reported among the individuals for whom we had report data, including academic (especially exam) pressures (35 [27%] individuals), bullying (28 [22%]), bereavement (36 [28%]), suicide in family or friends (17 [13%]), physical health conditions (47 [36%]), family problems (44 [34%]), social isolation or withdrawal (33 [25%]), child abuse or neglect (20 [15%]), excessive drinking (34 [26%]), and illicit drug use (38 [29%]). Suicide-related internet use was recorded in 30 (23%) cases. In the week before death 13 (10%) individuals had self-harmed and 35 (27%) had expressed suicidal ideas. 56 (43%) individuals had no known contact with health-care and social-care services or justice agencies.

2016 Shalit looked at the association between cannabis use and suicidality among men and women. They found that cannabis use, especially daily use, was significantly associated with increased incidence of suicidality among men but not among women. Conversely basal suicidality was associated with initiation of cannabis use among women but not men.

2016 Wright et al investigated marijuana use, behavioural approach and depressive symptoms in adolescents and young adults. 84 participants, 42(MJ) users and 42 controls aged 18-25 were balanced for gender. MJ group predicted increased depressive symptoms. Decreased fun-seeking, reward response, were predicted by MJ group. Gender predicted decreased reward responsiveness in females and decreased BIS in females. Female marijuana users had increased anxiety symptoms and increased disinhibition . Increased cotinine predicted increased drive and reward responsiveness. Apathy and Executive Dysfunction were not predicted by any measures. All results had small effect sizes.

2016 Henry et al looked at the intergenerational continuity in cannabis use. Fathers who began using cannabis by age 15 were more likely to meet the criteria for a lifetime cannabis disorder. The offspring of fathers who met the criteria for a disorder had higher odds of early initiation of cannabis use. Early-onset cannabis use by father was indirectly associated with their child's onset of cannabis use via father's lifetime cannabis disorder. No significant effects for mothers were observed, although analyses were limited due to the low rate of mothers who met the criteria for a lifetime cannabis disorder.

2016 Plunk et al looked at the impact of adolescent exposure to medical marijuana laws (MML) on high school completion, college enrolment and college degree completion. MMLs were associated with a 0.40 percentage point increase in the probability of not earning a high school diploma or GED after completing the 12th grade. High school MML exposure was also associated with a 1.84 and 0.85 percentage point increase in the probability of college non-enrollment and degree non-completion, respectively. Years of MML exposure exhibited a consistent dose response relationship for all outcomes. MMLs were also associated with 0.85 percentage point increase in daily marijuana use among 12th graders (up from 1.26%). Medical marijuana law exposure between 14 to 18 likely has a delayed effect on use and education that persists over time.

2016 Mason et al studied parent and peer pathways linking childhood experiences of abuse with marijuana use in adolescence and adulthood. 'Confirming elevated risk due to child maltreatment, path analysis showed that sexual abuse was positively related to adolescent marijuana use, whereas preschool abuse was positively related to adult marijuana use. In support of mediation, it was found that both forms of maltreatment were negatively related to parental attachment, which was negatively related, in turn, to having peers who use and approve of marijuana use. Peer marijuana approval/use was a strong positive predictor of adolescent marijuana use, which was a strong positive predictor, in turn, of adult marijuana use'.

2016 Mok et al looked at parental psychiatric disease and risks of attempted suicide and violent criminal offending in offspring. All persons born in Denmark 1967 – 1997 were followed from their 15th birthday till occurrence of adverse outcome or December 31st 2012 whichever came first.
'1 743 525 cohort members (48.7% female) Risks for offspring suicide attempt and violent offending were elevated across virtually the full spectrum of parental psychiatric disease. Incidence rate ratios were the most elevated for parental diagnoses of antisocial personality disorder (suicide attempt, risk 3.96 times; violent offending, 3.62 times; and cannabis misuse (suicide attempt, 3.57 times risk; violent offending, 4.05; and for parental suicide attempt (suicide attempt, 3.42;; violent offending, 3.31 times. Parental mood disorders (and bipolar disorder in particular) conferred more modest risk increases. A history of mental illness or suicide attempt in both parents was associated with double the risks compared with having just 1 affected parent. Associations between parental psychiatric disease and offspring violent offending were stronger for female than for male offspring, whereas little sex difference in risk was found for offspring suicide attempt'. Early interventions to tackle parental mental disorders may be beneficial to both parents and children.

2017 Kimbrel et al looked at suicide attempts in Iraq/Afghanistan veterans. 'The objective of the present research was to examine the association between lifetime cannabis use disorder (CUD), current suicidal ideation, and lifetime history of suicide attempts in a large and diverse sample of Iraq/Afghanistan-era veterans (N = 3233) using a battery of well-validated instruments. As expected, CUD was associated with both current suicidal ideation and lifetime suicide attempts, even after accounting for the effects of sex, posttraumatic stress disorder, depression, alcohol use disorder, non-cannabis drug use disorder, history of childhood sexual abuse, and combat exposure. Thus, the findings from the present study suggest that CUD may be a unique predictor of suicide attempts among Iraq/Afghanistan-era veterans; however, a significant limitation of the present study was its cross-sectional design.

2017 Gates et al investigated substance use, mental health disorders in prison and suicides. Abstract: Substance use disorders (SUD) and mental health disorders are significant public health issues that co-occur and are associated with high risk for suicide attempts. SUD and mental health disorders are more prevalent among offenders (i.e., prisoners or inmates) than the non-imprisoned population, raising concerns about the risk of self-harm. This cross-sectional study examined the population of a state prison system (10,988 out of 13,079) to identify associations among SUD (alcohol, cannabis, intravenous drugs, narcotics, and tobacco smoking), mental health disorders (anxiety, bipolar, depression, and psychotic disorders), and suicide attempts. The primary aim was to determine which groups (SUD, mental health disorders, and co-occurrences) were strongly association with suicide attempts. Groups with a documented SUD or mental health disorders compared to peers without these issues had 2.0 and 9.2 greater odds, respectively, for attempting suicide, which was significant for both conditions. There were also significant differences within SUD and mental health disorders groups in regard to suicide attempts. Groups with the greatest odds for suicide attempts were offenders with comorbid bipolar comorbid and anxiety, alcohol combined with depression, and cannabis co-occurring with depression. Documentation of suicide attempts during imprisonment indicates awareness, but also suggest a need to continue enhancing screening and evaluating environmental settings'.

2017 Guimaraes et al looked at criminal behaviour among illicit drug users (IDU). ' ACross-sectional study carried out with IDU undergoing treatment for chemical dependence. Of the total participants (n = 274), 46.7%, 15.7%, and 10.9% reported involvement in robbery, drug trafficking and homicide, respectively. Robbery was associated with young age, withdrawal symptoms, prison record, sex work, and crack use, while drug trafficking was associated with young age, low education, and marijuana use. Homicides were associated with cocaine and marijuana use'.

2017 Coentre et al examined suicidal behaviour and depression after first-episode psychosis. 'Depressive symptoms and suicidal behavior are common among patients that suffered a first-episode psychosis.. We included 19 studies from 12 countries, 7 studied depressive symptoms and 12 suicidal behavior. The

findings confirm that depressive symptoms and suicidal behavior have high rates in the years after first-episode psychosis….. Suicidal behavior was associated with previous suicide attempt, sexual abuse, comorbid polysubstance use, lower baseline functioning, longer time in treatment, recent negative events, older patients, longer duration of untreated psychosis, higher positive and negative psychotic symptoms, family history of severe mental disorder, substance use, depressive symptoms and cannabis use. Data also indicate that treatment and early intervention programs reduce depressive symptoms and suicidal behavior after first-episode psychosis'

2017 Bahorik et al looked at patterns of marijuana use among psychiatry patients with depression and its impact on recovery. Participants were 307 psychiatry outpatients with depression and past-month marijuana use. Longitudinal growth models examined patterns and predictors of marijuana use and its impact on symptom and functional outcomes. A considerable number of (40.7%; n=125) patients used marijuana within 30-days of baseline. Over 6-months, marijuana use decreased , but patterns varied by demographic and clinical characteristics. Depression symptoms contributed to increased marijuana use over the follow-up, and those aged 50+ increased their marijuana use compared to the youngest age group. Marijuana use worsened depression and anxiety symptoms; marijuana use led to poorer mental health functioning. Medical marijuana was associated with poorer physical health functioning.

2017 Libuy et al investigated the relative prevalence of schizophrenia among cannabis and cocaine users attending addiction services. 'A sample of 22,615 people treated for illicit drug use disorders was obtained from a national registry of addiction service users in Chile. Clinical diagnoses were established at admission to substance use treatment programs or at any point during the period of treatment. Prevalence rates of schizophrenia and related disorders, and affective disorders were calculated for the groups of people with cocaine use disorders, and cannabis use disorders. Odds ratios (OR) for schizophrenia and for affective disorders were calculated for cannabis users using the group of people treated for cocaine use disorders as reference category. They found that the prevalence of schizophrenia and related disorders was 1.1% in those with cocaine use disorders, but 5.2% in those with cannabis use disorders. The prevalence of affective disorders was 9.3% in cocaine use disorders, and 13.2% in cannabis use disorders. So the prevalence of schizophrenia and to a lesser extent affective disorders is higher among people with cannabis use disorder than cocaine use disorder among those attending addiction services'.

2017 Guvendiger et al looked at suicide attempts with substance abuse among those seeking treatment for cannabis use disorder. 'Numerous studies in youth and adults suggest strong association between substance use disorders and non-suicidal self-injury (NSSI) and suicidal behaviors. There is paucity of studies exploring the association of substance use with history of suicide attempts (HSA) and NSSI in children and adolescents in Turkey.

Participants were children and adolescents who were admitted to the Bakirkoy Trainee and Research Hospital for Psychiatric and Neurologic Disorders in Istanbul between January 2011 and December 2013. Two thousand five hundred eighteen participants were included. Questionnaires were applied to all patients. The association of NSSI and HSA with substance use, family characteristics, and subject characteristics were analyzed.The prevalence of NSSI and HSA behaviors among substance using youth in our sample were 52% and 21% respectively. Cannabis and cocaine use was found to be a significant risk factor for HSA, and polysubstance use was associated with both NSSI and HAS'.

2017 Miller et al looked at marijuana, violence and the law. Abstract:

'Marijuana is currently a growing risk to the public in the United States. Following expanding public opinion that marijuana provides little risk to health, state and federal legislatures have begun changing laws that will significantly increase accessibility of marijuana. Greater marijuana accessibility, resulting in more use, will lead to increased health risks in all demographic categories across the country. Violence is a well-publicized, prominent risk from the more potent, current marijuana available. We present cases that are highly popularized storylines in which marijuana led to unnecessary violence, health risks, and, in many cases, both. Through the analysis of these cases, we will identify the adverse effects of marijuana use and the role it played in the tragic outcomes in these and other instances. In the analysis of these cases, we found marijuana as the single most common, correlative variable in otherwise diverse populations and circumstances surrounding the association of violence and marijuana.

2017 Johnson et al investigated marijuana use and physical dating violence (PDV) among adolescents and emerging adults. They conducted a systematic review of the relevant literature between 2003 and 2015. 13 articles examined marijuana in association with PDV 5 addressed victimisation and 11 perpetration. They suggested that marijuana use is associated with an increase in the odds of PDV victimisation and 45% increase in odds of perpetration.

2017 Orpinas et al looked at perpetration of physical dating violence (PDV) 7-year associations with suicidal ideation, weapons and substance abuse. The Healthy Teens Longitudinal Study followed 588 randomly selected students adolescents from grades 6 – 12. They completed a self-reported computer-based survey every spring. Across most grades, Significantly more students in the 'Increasing' trajectory for PDV rather than 'Low' trajectory, reported suicidal ideation, carried a weapon and threatened someone with a weapon. Ehy also had higher trajectories of alcohol use, being drunk and marijuana use than the low trajectory. All differences were already significant in grade 6. So behaviour problems – PDV, suicide ideation and attempts, weapon carrying and threats, marijuana and alcohol use cluster together as early as 6th grade and persist over time.

2017 Rhew et al investigated early adolescent depression and the increased risk of cannabis and alcohol abuse. 521 youths from 12 to 15 were evaluated annually from sixth to ninth grade andagain at 18 years. At age 18, 20.9% of the cohort reported past-year cannabis use disorder and 19.8% reported past-year alcohol use disorder. One standard deviation increase in cumulative depression during early adolescence was associated with a 50% higher risk for cannabis use disorder. A similar association occurred between adolescent depression and alcohol use disorder but did not reach statistical significance.

2017 Agrawal et al looked at major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins. 'In 13 986 twins (6181 monozygotic and 7805 dizygotic), cannabis use ranged from 1345 (30·4%) of 4432 people in sample 1 to 2275 (69·0%) of 3299 in sample 3. Mean age of first cannabis use ranged from 17·9 years (SD 3·3) in sample 3 to 21·1 years (5·2) in sample 1, and frequent use (≥100 times) was reported by 214 (15·9%) of 1345 users in sample 1 and 499 (21·9%) of 2275 in sample 3. The prevalence of suicidal ideation ranged from 1102 (24·9%) of 4432 people in sample 1 to 1644 (26·3%) of 6255 people in sample 2 and 865 (26·2%) of 3299 people in sample 3. Prevalence of MDD ranged from 901 (20·3%) people in sample 1 to 1773 (28·3%) in sample 2. The monozygotic twin who used cannabis frequently was more likely to report MDD (odds ratio 1·98, 95% CI 1·11–3·53) and suicidal ideation (2·47, 1·19–5·10) compared with their identical twin who had used cannabis less frequently, even after adjustment for covariates. For early cannabis use, the monozygotic point estimate was not significant but could be equated to the significant dizygotic estimate, suggesting a possible association with suicidal ideation'

2017 Borges et al looked at alcohol, cannabis etc and subsequent suicide ideation ideation and attempt among young Mexicans. "We estimated prospective associations of substance use as a risk factor for incident suicide ideation and attempt, from a follow-up conducted in 2013 (n = 1071) of the original Mexican Adolescent Mental Health Survey conducted in 2005. RESULTS:

Cannabis use before age 15 (ideation risk ratio RR) = 3.97; (attempt RR) = 5.23; early onset of DSM-IV drug use disorder (DUD) among cannabis users (ideation RR = 3.30); (attempt RR = 4.14); high frequency of cannabis use (RR for attempts = 4.60;) and recent DSM-IV-DUD among cannabis users (RR for attempts = 4.74;) increased the RR. For "other drug use", significant results were found among those with high frequency use of other drugs such that they had a higher RR of suicide attempt (5.04). For alcohol, only those who initiated alcohol before age 15 had higher RRs of suicide attempt (1.79;).

Those who used cannabis at an early age, early onset of DSM-IV-DUD, and those with heavy cannabis use and recent DSM-IV-DUD among cannabis users in the last 12-months had increased risk of suicide ideation and attempt. Drugs other than cannabis showed some of these associations, but to a lesser degree".

2017 Dierker et al looked at depression and marijuana use disorder symptoms among current marijuana users. 'Depression is one of the most consistent risk factors implicated in both the course of escalating substance use behaviors and in the development of substance dependence symptoms, including those associated with marijuana use. In the present study, we evaluate if depression is associated with marijuana use disorder symptoms across the continuum of marijuana use frequency. Data were drawn from six annual surveys of the National Survey of Drug Use and Health to include adults who reported using marijuana at least once in the past 30days (N=28,557). After statistical control for sociodemographic characteristics and substance use behaviours including marijuana use, alcohol use, smoking, and use of illicit substances other than marijuana, depression was positively and significantly associated with each of the marijuana use disorder symptoms as well as the symptom total score. Adult marijuana users with depression were consistently more likely to experience marijuana use disorder symptoms and a larger number of symptoms, with the magnitude and direction of the relationship generally consistent across all levels of marijuana use frequency from 1day used in the past month to daily marijuana use'.

2017 Dugre et al looked at the persistency of cannabis use predicting violence following acute psychiatric discharge. 'Violence is a major concern and is prevalent across several mental disorders. The use of

substances has been associated with an exacerbation of psychiatric symptoms as well as with violence. Compared to other substances such as alcohol and cocaine, existing literature on the cannabis–violence relationship has been more limited, with most studies being conducted in the general population, and has shown controversial results. Evidence has suggested a stronger relationship when examining the effects of the persistency of cannabis use on future violent behaviors. Though, while cannabis use is highly prevalent amid psychiatric patients, far less literature on the subject has been conducted in this population. Hence, the present prospective study aims to investigate the persistency of cannabis use in psychiatric patients. The sample comprised of 1,136 recently discharged psychiatric patients provided by the MacArthur Risk Assessment Study. A multi-wave (five-assessment) follow-up design was employed to allow temporal sequencing between substance use and violent behaviors. Generalized estimating equations (GEE) were used to examine the effect of persistency of cannabis use on violence, while controlling for potential confounding factors. Potential bidirectional association was also investigated using the same statistical approach. Our results suggest a unidirectional association between cannabis use and violence. GEE model revealed that the continuity of cannabis use across more than one time wave was associated with increased risks of future violent behavior. Patients who reported having used cannabis at each follow-up periods were 2.44 times more likely to display violent behaviors (OR = 2.44, 95% CI: 1.06–5.63, $p < 0.05$). These findings are particularly relevant as they suggest that the longer individuals report having used cannabis after a psychiatric discharge, the more likely they are of being violent in the following time waves. These results add to our understanding of the negative consequences of chronic cannabis use amid psychiatric patients'.

2018 Dawson et al investigated violent behaviour by emergency department patients with an involuntary hold status. Abstract: Retrospective review of patients evaluated during an involuntary hold at a suburban acute care hospital ED from January 2014 through November 2015. Of 251 patients, 22 (9%) had violent incidents in the ED. Violent patients were more likely to have a urine drug screen positive for tricyclic antidepressants (18.2% vs 4.8%, P=0.03) and to present with substance misuse (68.2% vs 39.7%, P=0.01), specifically with marijuana (22.7% vs 9.6%, P=0.06) and alcohol (54.5% vs 24.9%, P=0.003). ED readmission rates were higher for violent patients (18.2% vs 3.9%, P=0.02). No significant difference was found between violent patients and nonviolent patients for sex, race, marital status, insurance status, medical or psychiatric condition, reason for involuntary hold, or length of stay.

2018 Pro et al Looked at microaggressions and marijuana use among college students. Abstract:
This study examines the association between exposure to microaggressions and marijuana use, using original survey data from a sample of racial/ethnic minority college students (n = 332) from a large Division I university in the United States. Nearly all of our sample (96%) reported at least one experience with microaggressions in the past 6 months, while 33% reported using marijuana regularly. We modeled regular use of marijuana using multiple logistic regression, with consideration of sex, age, race/ethnicity, and microaggression scale scores as covariates. Age, sex, the microinvalidations subscale score, and the full microaggression scale score were significantly associated with marijuana use in our full models ($p < .01$; $p = .01$; $p = .02$; $p = .03$, respectively). With each additional experience of microaggression, the odds of regular marijuana use increase. Academic communities may consider the primary prevention of discriminatory behavior when addressing student substance use.

2018 Moulin et al looked to see if cannabis is a significant risk factor for violent behaviour in the early phase psychosis. **Absratct:** Previous literature suggests that prevalence of cannabis use in the early phase of psychosis is high, and that early psychosis patients are at high-risk for violent behavior. However, the link between cannabis use and violent behavior in early psychosis patients is unclear. We carried out a study on a sample of early psychosis patients, in order to explore the impact of cannabis use on the risk of violent behavior (VB), while taking into account (1) potential confounding factors and, (2) interactions with other dynamic risk factors of VB. In a sample of 265 early psychosis patients, treated at the Treatment and Early Intervention in Psychosis Program (TIPP) in Lausanne, we used logistic regression models to explore the link between various dynamic risk factors of VB [positive symptoms, substance use disorder (drugs including cannabis, alcohol and others drugs), insight, impulsivity, affective instability, and treatment adherence], and VB occurring during treatment. In order to understand hierarchical effects attributable to the combinations of risk factors on VB we conducted a Classification and Regression Tree (CART). Our results show that cannabis use disorder is a risk factor for VB. The associations among risk factors suggest the presence of two patient profiles with an increased rate of VB: the first is composed of patients with cannabis use disorder and impulsivity, and the second of patients combining cannabis use disorder, absence of insight and non-adherence to treatment. The results also show the moderating role of insight and adherence to treatment on the rate of VB in patients with cannabis use disorder.This study suggests that cannabis use disorder is a significant risk factor for VB amongst early psychosis patients, particularly when

combined with either impulsivity, lack of insight and non-adherence to treatment. These results suggest that preventive strategies could be developed on the basis of such patient profiles.

2018 Subramaniam et al Studied orbo-frontal connectivity and its association with depression and anxiety in marijuana using adolescents. Abstract: Prevalence of marijuana (MJ) use among adolescents has been on the rise. MJ use has been reported to impact several brain regions, including frontal regions such as the orbitofrontal cortex (OFC). The OFC is involved in emotion regulation and processing and has been associated with symptoms of depression and anxiety. Therefore, we hypothesized that adolescent MJ users would show disruptions in OFC connectivity compared with healthy adolescents (HC) which would be associated with symptoms of mood and anxiety. 43 MJ-using and 31 HC adolescents completed clinical measures including the Hamilton Anxiety Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D). Resting-state functional magnetic resonance imaging data was also acquired for all participants. In MJ users, increased depressive symptoms were associated with increased connectivity between the left OFC and left parietal regions. In contrast, lower ratings of anxiety were associated with increased connectivity between right and left OFC and right occipital and temporal regions. These findings indicate significant differences in OFC connectivity in MJ-using adolescents, which correlated with mood/anxiety. Future studies with an increased number of female participants is required to address potential sex differences in connectivity patterns related to symptoms of depression and anxiety. This study highlights the association between OFC connectivity, MJ use, and symptoms of depression and anxiety in adolescents. These findings provide further insight into understanding the neural correlates that modulate the relationship between comorbid MJ use and mood disorders and could potentially help us better develop preventive and treatment measures.

2019 Chadi et al investigated depressive symptoms and suicidality in adolescents using e-cigarettes and marijuana. Abstract: E-cigarette use has increased dramatically among adolescents in the past 5 years alongside a steady increase in daily use of marijuana. This period coincides with a historic rise in depression and suicidal ideation among adolescents. In this study, we describe the associations between e-cigarette and marijuana use and depressive symptoms and suicidality in a large nationally representative sample of high school students. We used data from the 2 most recent waves (2015 and 2017) of the Youth Risk Behavior Survey. Our sample (n = 26,821) included only participants with complete information for age, sex, race/ethnicity, and exposure to e-cigarettes and marijuana (89.5% of survey respondents). We performed multivariate logistic regressions to explore the associations between single or dual use of e-cigarette and marijuana and depressive and suicidal symptoms in the past year adjusting for relevant confounders. E-cigarette-only use was reported in 9.1% of participants, marijuana-only use in 9.7%, and dual e-cigarette/marijuana use in 10.2%. E-cigarette-only use (vs no use) was associated with increased odds of reporting suicidal ideation (adjusted odds ratio [AOR]:1.23, 95% CI 1.03–1.47) and depressive symptoms (AOR: 1.37, 95% CI 1.19–1.57), which was also observed with marijuana-only use (AOR: 1.25, 95% CI 1.04–1.50 and AOR: 1.49, 95% CI 1.27–1.75) and dual use (AOR: 1.28, 95% CI 1.06–1.54 and AOR: 1.62, 95% CI 1.39–1.88). Youth with single and dual e-cigarette and marijuana use had increased odds of reporting depressive symptoms and suicidality compared to youth who denied use. There is a need for effective prevention and intervention strategies to help mitigate adverse mental health outcomes in this population.

2019 Gobbi et al looked for an association between cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood Abstract: Longitudinal and prospective studies, assessing cannabis use in adolescents younger than 18 years (at least 1 assessment point) and then ascertaining development of depression in young adulthood (age 18 to 32 years) were selected, and odds ratios (OR) adjusted for the presence of baseline depression and/or anxiety and/or suicidality were extracted. Study quality was assessed using the Research Triangle Institute item bank on risk of bias and precision of observational studies. Two reviewers conducted all review stages independently. Selected data were pooled using random-effects meta-analysis.The studies assessing cannabis use and depression at different points from adolescence to young adulthood and reporting the corresponding OR were included. In the studies selected, depression was diagnosed according to the third or fourth editions of Diagnostic and Statistical Manual of Mental Disorders or by using scales with predetermined cutoff points. After screening 3142 articles, 269 articles were selected for full-text review, 35 were selected for further review, and 11 studies comprising 23 317 individuals were included in the quantitative analysis. The OR of developing depression for cannabis users in young adulthood compared with nonusers was 1.37 (95% CI, 1.16-1.62; $I2 = 0\%$). The pooled OR for anxiety was not statistically significant: 1.18 (95% CI, 0.84-1.67; $I2 = 42\%$). The pooled OR for suicidal ideation was 1.50 (95% CI, 1.11-2.03; $I2 = 0\%$), and for suicidal attempt was 3.46 (95% CI, 1.53-7.84, $I2 = 61.3\%$).Although individual-level risk remains moderate to low and results from this study should be confirmed in future adequately powered prospective studies, the high prevalence of adolescents consuming cannabis generates a large number of young people who could

develop depression and suicidality attributable to cannabis. This is an important public health problem and concern, which should be properly addressed by health care policy.

2019 (January) Alex Berenson wrote a book: 'Tell your children the truth about marijuana, mental illness and violence'. He writes: My wife Jacqueline is a forensic psychiatrist. She evaluates the criminally mentally ill. She told me that nearly all her patients had used marijuana heavily, many at the times of their crimes. At first I didn't really believe her—stupidly—but she encouraged me to evaluate the evidence myself. And the more I read, the more I realized she was right. Marijuana drives a surprising amount of psychosis, and psychosis—besides being a terrible burden for sufferers and their families—is a shockingly high risk for violent crime.
Psychosis is a known factor for violent crime. People with schizophrenia commit violent crime at rates far higher than healthy people - their homicide rates are about 20 times as high. Worse, they commit most of that crime while they are under the influence. Since cannabis causes paranoia—not even advocates dispute that fact—and psychosis, it is not surprising that it would drive violent crime. And in fact there are a number of good studies showing that users have significantly higher violence rates than non-users. Further, in researching the book, I found many, many cases where the causation appeared clear. In some cases it was as simple and obvious as, *this person—with no history of violence*—smoked, became psychotic, and committed a homicide.

2019 Dellazizzo et al looked at cannabis use and violence in patients with severe mental illness. The relationship between cannabis and violence remains unclear, especially amid those with severe mental illnesses (SMI). The objective of this meta-analysis was to investigate the cannabis-violence association in a population of individuals with a SMI. A systematic search of literature using PubMed, PsychINFO, Web of Science and Google scholar was performed (any time-August 2018). All peer-reviewed publications assessing both cannabis use and the perpetration of violence in an SMI sample were included. Data on several key study characteristics such as the proportion of SMI in the sample as well as the number of cannabis users and violent participants were extracted. Odds ratios (OR) were likewise extracted and aggregated with random-effects models. Of the potential 2449 articles that were screened for eligibility, 12 studies were analyzed using a random-effect meta-analysis. Results showed a moderate association between cannabis use and violence (OR = 3.02, CI = 2.01–4.54, $p = 0.0001$). The association was significantly higher when comparing cannabis misuse (OR = 5.8, CI = 3.27–10.28, $p = 0.0001$) to cannabis use (OR = 2.04, CI = 1.36–3.05, $p = 0.001$). These findings are clinically relevant for violence prevention/management and highlight the necessity of further investigations with methodologically-sound studies. Thus, longitudinal studies adjusting for important confounding factors (i.e., psychopathic traits and stimulant use) are warranted.

2019 Maciel et al looked a t physical violence during pregnancy in France. Abstract: Objectives Even during pregnancy women may suffer from violence. We estimated the prevalence of physical abuse during pregnancy, we analyzed the main risk factors and described the relationship between physical violence, psychological wellbeing and pregnancy outcome. Methods We used a national representative sample of births, in all public and private maternity units, in 2016 in France. Women were interviewed after delivery, on their living conditions and occurrence of physical violence at least once during pregnancy. The study of risk factors and pregnancy outcome was done with multivariable logistic regressions. Results Of 12,330 women included in the analysis 1.8% (95% CI 1.6-2.0) had been exposed to physical violence during pregnancy. Risk of violence was associated with the couple situation [women without a partner or in couple not cohabiting (OR 2.89, 95% CI 1.96-4.26)], household income (less than 3000 euros monthly), and state medical assistance coverage. Physical violence was more prevalent in case of a history of induced abortion or cannabis use during pregnancy. Psychological distress was more frequent with than without physical violence (e.g., 62% vs. 24% had a sadness period during pregnancy, $p < 0.001$). The risk of spontaneous preterm birth and transfer of the newborn to a neonatal intensive care unit were significantly higher among women experiencing physical violence during pregnancy compared to other women. Conclusions for Practice Main factors associated with increased risk of violence during pregnancy were socio-economics. The identification by caregivers of women exposed to violence during pregnancy needs to be improved to develop preventive and care strategies.

2019 Cheslack-Postava et al examined increasing depression and substance abuse among former smokers in the United States fro 2002 to 2016. Mental health and substance use problems are associated with smoking relapse among former smokers. Yet, little is known about the prevalence of mental health and substance use among former smokers in the U.S. In addition, it is unknown whether the prevalence of these conditions has changed over time as former U.S. smokers have grown to outnumber current U.S. smokers. This study, which was conducted in 2018 and 2019, examined the prevalence and trends over time in

depression (2005–2016), marijuana use (2002–2016), and alcohol use problems (2002–2016) among former U.S. smokers.The National Survey on Drug Use and Health is an annual, nationally representative, cross-sectional study. Data from U.S. individuals who were aged ≥18 years in 2002–2016 were included. Former smokers were defined as having smoked ≥100 lifetime cigarettes and no past-year cigarettes.From 2005 to 2016, the prevalence of major depression increased from 4.88% to 6.04% (AOR=1.01, 95% CI=1.00, 1.03, p=0.04). From 2002 to 2016, past-year marijuana use rose from 5.35% to 10.09% (AOR=1.08, 95% CI=1.07, 1.09, p<0.001) among former smokers. Past-month binge alcohol use also increased from 17.22% to 22.33% (AOR=1.03, 95% CI=1.02, 1.04, p<0.001), although the prevalence of past-year alcohol abuse or dependence did not change.Depression and substance use, which are factors associated with increased risk for cigarette use relapse, appear to be increasing over time among former U.S. smokers. Increased awareness of these trends may be important for clinical and public health efforts to direct attention to conditions potentially threatening sustained abstinence among former smokers.

2019 Carvalho et al looked at cannabis use and suicide attempts in adolescents from 21 low-middle-income countries. Abstract: BACKGROUND:
Evidence suggests that cannabis use may be associated with suicidality in adolescence. Nevertheless, very few studies have assessed this association in low- and middle-income countries (LMICs). In this cross-sectional survey, we investigated the association of cannabis use and suicidal attempts in adolescents from 21 LMICs, adjusting for potential confounders. METHOD: Data from the Global school-based Student Health Survey was analyzed in 86,254 adolescents from 21 countries [mean (SD) age = 13.7 (0.9) years; 49.0% girls]. Suicide attempts during past year and cannabis during past month and lifetime were assessed. Multivariable logistic regression analyses were conducted. RESULTS:The overall prevalence of past 30-day cannabis use was 2.8% and the age-sex adjusted prevalence varied from 0.5% (Laos) to 37.6% (Samoa), while the overall prevalence of lifetime cannabis use was 3.9% (range 0.5%-44.9%). The overall prevalence of suicide attempts during the past year was 10.5%. Following multivariable adjustment to potential confounding variables, past 30-day cannabis use was significantly associated with suicide attempts (OR = 2.03; 95% CI: 1.42-2.91). Lifetime cannabis use was also independently associated with suicide attempts (OR = 2.30; 95% CI: 1.74-3.04). CONCLUSION:Our data indicate that cannabis use is associated with a greater likelihood for suicide attempts in adolescents living in LMICs. The causality of this association should be confirmed/refuted in prospective studies to further inform public health policies for suicide prevention in LMICs.

2019 Allan et al investigated the interactive effects of PTSD and substance use on suicidal ideation and behaviour in military personnel and the increased risk from marijuana use. Abstract: The current study examines the unique and interactive effects of posttraumatic stress disorder (PTSD) symptoms and days using alcohol, opioids, and marijuana on PTSD symptoms, suicidal ideation, and suicidal behavior up to 1 year, later in a high-risk sample of military personnel not active in mental health treatment. Methods Current and former military personnel at risk for suicide (N = 545; M age = 31.91 years, standard deviation = 7.27; 88.2% male) completed self-report measures of PTSD symptoms, past 30 days heavy alcohol use, opioid use, marijuana use, and current suicidal ideation via telephone at baseline and 1, 3, 6, and 12 months later. PTSD symptoms and the substance use variables (and relevant covariates) were entered as predictors of changes in PTSD symptoms, the likelihood of suicidal ideation, suicidal ideation severity, and the likelihood of suicidal behavior during the 11-month follow-up period. Results PTSD symptoms predicted PTSD symptoms 1 month later. PTSD symptoms and marijuana use predicted the likelihood of suicidal ideation 1 month later and suicidal behavior during the 11-month follow-up period. The interaction between PTSD symptoms and marijuana use significantly predicted increased PTSD symptoms over time and suicidal behavior. At high, but not low levels of PTSD symptoms, more days using marijuana predicted increased PTSD symptoms over time and the likelihood of suicidal behavior. Conclusions: Results suggest marijuana, especially for military personnel experiencing elevated PTSD symptoms may negatively impact suicidal thoughts and behavior. These results are relevant to suggestions that medical marijuana could be used in treating or augmenting treatment for PTSD.

2020 Meir et al looked at the associations between recent and cumulative cannabis use and internalizing problems in boys from adolescence to young adulthood. Abstract: This study tested whether increases in recent and cumulative cannabis use were each associated with increases in internalizing problems from adolescence to young adulthood. Participants were boys from a community sample that was assessed annually from ~age 15-26 (N = 506). Boys reported on their cannabis use, depression symptoms, and anxiety/depression problems each year. Exposures were frequency of cannabis use in a given year (no use, < weekly use, weekly or more frequent use) and cumulative prior years of weekly cannabis use. Outcomes were depression symptoms and anxiety/depression problems in a given year. Analyses examined within-person associations between changes in exposures and outcomes over time, which eliminated "fixed"

(unchanging) individual differences as potential confounds. Analyses also accounted for time-varying factors as potential confounds (other substance use, externalizing problems, subclinical psychotic symptoms). Results showed that increases in recent cannabis use and cumulative prior years of weekly cannabis use were each associated with increases in depression symptoms and anxiety/depression problems. After controlling for time-varying covariates, increases in cumulative prior years of weekly cannabis use, but not recent cannabis use, remained associated with increases in depression symptoms and anxiety/depression problems. Specifically, each additional year of prior weekly cannabis use was associated with a small increase in depression symptoms *(b* = 0.012, p = .005) and anxiety/depression problems (b = 0.009, p = .001). Associations did not vary systematically across time. There was also no evidence of reverse causation. As boys engaged in weekly cannabis use for more years, they showed increases in internalizing problems, suggesting the importance of preventing chronic weekly cannabis use.

2020 Dellazizzo et al looked at the association between the use of cannabis and physical violence in youths. The aim of this meta-analysis was to investigate the extent to which cannabis use among youths is associated with the risk of perpetrating physical violence. Searches were conducted in PubMed, PsycINFO, Web of Science, and Google Scholar for articles published from the inception of each database to July 2019. All studies that examined both cannabis use and the perpetration of physical violence in a sample of youths and young adults <30 years old were included. The meta-analysis was performed with a random-effects model. Risk of publication bias was assessed with Egger's test. Guidelines from the Meta-Analysis of Observational Studies in Epidemiology were followed. Results: After screening 11,348 potential studies, 30 study arms were included, yielding a total of 296,815 adolescents and young adults. The odds ratio for the pooled studies was 2.11 (95% CI=1.64, 2.72). The pooled odds ratios were 2.15 (95% CI=1.58, 2.94) and 2.02 (95% CI=1.26, 3.23) for the cross-sectional and longitudinal studies, respectively. Preliminary evidence suggests that the risk of violence was higher for persistent heavy users (odds ratio=2.81, 95% CI=1.68, 4.74) compared with past-year users (odds ratio=2.05, 95% CI=1.5, 2.8) and lifetime users (odds ratio=1.94, 95% CI=1.29, 2.93). The odds ratio for unadjusted studies was 2.62 (95% CI=1.89, 3.62), and for studies using odds ratios adjusted for potential confounding factors, 2.01 (95% CI=1.57, 2.56). Conclusions: These results demonstrate a moderate association between cannabis use and physical violence, which remained significant regardless of study design and adjustment for confounding factors (i.e., socioeconomic factors, other substance use). Cannabis use in this population is a risk factor for violence.

2020 Hengartner et al looked at Cannabis use during adolescence and the occurrence of depression, suicidality and anxiety disorder across adulthood. A stratified population-based cohort of young adults (n = 591) from Zurich, Switzerland, was retrospectively assessed at age 19/20 for cannabis use in adolescence. The occurrence of depression, suicidality and anxiety disorders was repeatedly assessed via semi-structured clinical interviews at the ages of 20/21, 22/23, 27/28, 29/30, 34/35, 40/41, and 49/50. Associations were controlled for various covariates, including socio-economic deprivation in adolescence as well as repeated time-varying measures of substance abuse during adulthood. **Results:** About a quarter (24%) reported cannabis use during adolescence; 11% started at age 15/16 or younger and 13% between the ages of 16/17 and 19/20. In the adjusted multivariable model, cannabis use during adolescence was associated with adult depression (aOR = 1.70, 95%-CI = 1.24-2.32) and suicidality (aOR = 1.65, 95%-CI = 1.11-2.47), but not anxiety disorders (aOR = 1.10, 95%-CI = 0.82-1.48). First use at age 15/16 and younger (as against first use between age 16/17 and 19/20 and no use) and frequent use in adolescence (as against less frequent use and no use) were associated with a higher risk of depression in adult life.**Conclusions:** In this longitudinal cohort study over 30-years, cannabis use during adolescence was associated with depression and suicidality in adult life. Young age at first use and high frequency of use in adolescence may particularly increase the risk of depression in adulthood. All associations were independent of cannabis abuse and other substance abuse during adulthood

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Cannabis and Driving

Tests of car-driving on tracks free of other vehicles by Klonoff 1974, Hansteen 1976 and Attwood 1981, using low or even very low doses of THC, found slight to moderate impairment of driving ability.

Cannabis intoxication affects mental functions in the same way, whether the user is just starting, or is a regular smoker. Moscowitz, a leading researcher in this field, reported in 1985 that, even in *moderate doses*, cannabis use impairs the functions of co-ordination, tracking (following a randomly moving obstacle with an instrument), perception and vigilance. He proceeded to test drivers on car simulators and confirmed his findings. Moscowitz, Miller and Branconnier (1983) all recorded a deterioration of the ability to assess time accurately and an impairment of short-term memory. Although probably not of prime importance in driving cars, these deficiencies would be of vital significance in an airline pilot. Smiley (1986) using higher doses, suddenly placed an obstacle in the path of drivers on simulators and found several were unable to avoid a crash.

In an experiment on reaction times, Wilson and others in 1993 demonstrated that a clear association exists between the dose of cannabis (15-35mg) and reaction times.

In 1994, WHJ Robbe, of The University of Limburg in Maastricht, studied drivers who had taken 20 milligrams of THC - a very low dose. A single one-gram cigarette today can contain anything up to 200 milligrams. He found a significant deterioration in driving ability, especially keeping the car steady in the middle of a lane and a constant distance from the verge. He also discovered that, comparing the 20mg cannabis dose to a blood alcohol level of 1g/litre of blood (just over the legal limit) in identical studies, the results were very close as regards the deterioration in each variable.

Several researchers, including Robbe and Capel and Pliner 1973, have found on doing these kinds of experiments that, if strongly motivated, drivers can, barring distractions or unexpected complications, compensate for some of the impairments. The dangers posed by cannabis in a *real* situation, may therefore be underestimated.

And in 1995 Chesher tested car-driving ability in placebo-controlled studies in real traffic situations and dose-related performance decrements *were* recorded. An American study in 1988 by Carl Soderstrom et al, reported that, although 9 to 10 times as many people in the United States drink alcohol, cannabis is implicated in a similar number of accidents.

Janowsky used experienced airline pilots on flight simulators to investigate the problem. In 1976, despite the low dose (eight milligram) involved, the subsequent deterioration in short-term memory caused them to make mistakes. Confirmation came in 1991 in a well-publicised study by Leirer et al of Stanford, California. Using a dose of 20 milligrams THC, in a double-blind experiment, they found that the performance was worse in all aspects of flying, even up to and beyond 24 hours after consumption, and the pilots were totally unaware of a problem.
Someone taking a joint today *should not* be driving tomorrow.

Tests on driving were carried out by a BBC team for a Five Live Report, "The Drug Drivers" on 30th December 2001. Radar equipment linked to satellites monitored the driving skills of a 32-year-old woman before and after she smoked a joint. There was a marked decline of her reaction times and in her overall competence. At 66 mph, she took on average of 4.6 seconds to come to a halt over 270 feet. After a joint her time increased to 5.35 seconds and the stopping distance to 308.5 feet. A sobriety test was failed almost an hour later.

Analysing blood samples from accident victims is an approach that some researchers have used. In 1988, Dr Dale Gieringer found that "Significant blood levels of THC occur 3 to 5 times more frequently in fatally injured drivers than in the normal population".

In 1980 Warren et al, researching in Ontario, found that those who drove under the influence of cannabis were almost twice as likely to be involved in an accident.

In 1990 this information was up-dated by Cimbura and others. He found that, of 1169 fatally injured drivers and 225 pedestrians between 1982 and 1984 in Ontario, THC was present in the blood of 10.9% of the drivers and 7.6% of the pedestrians, ethanol in 57.1% of drivers and 53.3% of pedestrians. This is a threefold increase in blood THC levels since the 1980 study.

1999 saw a report in The Canadian Journal of Public Health by Walsh et al, stating that cannabis is the most frequent illicit drug found in drivers killed or injured in motor vehicle collisions in Ontario, with 22.8% of drivers admitting driving under its influence.

Nearer home in Scotland in the same year, 1999, in a four-year period from 1995 to 1998, the Department of Forensic Medicine and Science (Seymour and Oliver) received 752 samples from drivers suspected of driving under the influence of drink or drugs in the Strathclyde region. Drugs were detected in 68% and 90% of blood and urine samples respectively.
Cannabis was the most frequent occurring in 39% of all positive blood samples.

Analysis of blood to quantify the amount of the drug "needed" to make driving hazardous was carried out in 1993 in a study of truck driver fatalities by Crouch and others. They concluded that marijuana use was a factor in all cases where the delta-9-THC content exceeded 1.0ng/ml of blood and alcohol where the blood/alcohol concentration was 0.04% wt/vol or greater. In 50 of 56 cases where psychoactive drugs or alcohol were found, impairment due to substance abuse contributed to the fatal accident.

Ramaekers et al in 2004 using more modern techniques for blood analysis, found an ever-stronger link between cannabis consumption before or during driving and an increased risk of accidents than previously thought. He found that drivers under the influence were 3 to 7 times more likely to be the cause of accidents in which they were involved.

Researchers have repeatedly warned that, since alcohol affects the psychomotor functions fairly quickly, and cannabis the cognitive ones, the combination will undoubtedly be extremely dangerous, especially in a complex traffic situation. In 2002 Ramaekers team carried out a study and showed that moderate amounts of alcohol and moderate amounts of cannabis can together cause a very strong increase in the risk of making a driving error.

Differences in countries are apparent in this respect. In a 1986 USA survey by McBay, 75% of a sample of drivers involved in accidents had cannabinoids and alcohol in their blood. In Australia only 50% of the surviving drivers of dangerous or fatal collisions had this combination (Road Safety 1995) and in Norway (Gjerde 1991) 56% of drug impaired drivers were negative for alcohol but positive for THC.

In their 1997 report on cannabis the WHO said that cannabis increases the risk of motor vehicle accidents and the risk is much higher with a combination of cannabis and alcohol.

A French study in 2003 by Mura et al took blood from 900 injured road traffic accident victims and compared it with blood from 900 controls at the same A and E departments but not for traffic accidents. The most common drug detected was alcohol but for cannabis alone (no other drug in the system) 10% of drivers tested positive and only 5% of the controls.

The BMJ in December 2005 carried a paper by French scientists led by Bernard Laumon. From 10,748 fatal car crashes between 2001 and 2003 they investigated the 6766 drivers held to be responsible for the accident. The controls were 3006 of the other drivers. Taking into account the age of the vehicle and age of driver, the researchers concluded that cannabis caused a significant number of the fatalities. 681(7%) tested positive for cannabis and 2096 (21.4%) for alcohol. Cannabis was deemed directly responsible for 2.5% and alcohol 29% of the crashes. A combination of cannabis and alcohol was held to be 16 times more risky than either drug alone.

Another factor to consider is that, cannabis users erroneously think they have "sobered up" long before they really have, so they may well drive before they should. In a survey at Glasgow University, at the beginning of 2001, it was reported that one in 10 young people between 17 and 39 regularly drove under the influence of drugs, 75% after smoking cannabis. They were also quite happy to take a lift from friends who had just taken drugs. A huge six-fold increase in road crash victims found with illegal drugs in their systems sparked off this study of 1000 drivers. One "spliff" is thought by some experts to have the same effect as the amount of alcohol needed to just exceed the drink-drive limit. The biggest problem was among men between the ages of 20 and 24. There are now increased calls for reliable roadside testing for drugs to be introduced. The difficulty here is to ascertain when the drug was actually taken. In the case of cannabis, the consumption of a joint only once a month or even less frequently, will give consistently positive results. Blood levels of THC may prove useful in this respect.

A month later, an Internet study was conducted for 'Max Power' a motoring magazine for young people, especially aimed at men between 17 and 24. This revealed an even more alarming 27% of youngsters regularly driving at least once a week while under the influence of drugs; most of them boasting that their driving skills actually improved, 36% confessed to a monthly occurrence. Cannabis was, by far, the commonest drug taken. The Daily Mail reported on 23rd April 2006 that another survey for "Max Power" had revealed a huge increase in these figures. Nearly half of the 447 youngsters interviewed admitted to driving regularly after having taken drugs like ecstasy or cocaine, one in five said it was a daily occurrence. They were confident of escaping detection because of the lack of roadside tests which are not due to be in use for about 2 years.

An analysis of the 2003 Monitoring the Future and Census Bureau data in the USA showed the following results: Out of nearly 4 million high school seniors in America, it was estimated that approximately one in six i.e. 600,000 drove under the influence of marijuana, nearly the same as for alcohol, 640,000. An estimated 38,000 reported they had crashed while under its influence in 2001, 46,000 while affected by alcohol.

Many youngsters seemed totally ignorant of the law, they were not aware that it is an offence to drive under the influence of drugs, as it is with alcohol.

In 2002 a paper from New South Wales (O'Kane et al) in Australia reported, " The incidence of driving while affected by cannabis is rising in parallel with increasing cannabis use in the community. Young drivers are at particular risk. Improvements in research, methodology, technical and laboratory testing methods have occurred in the last 10 years. …Studies now show that cannabis has a significant impairing effect on driving when used alone and that this effect is exaggerated when combined with alcohol. Of particular concern is the presence of cannabis as sole psychiatric drug in an increasing number of road fatalities".

2004 Raemakers et al did a review of driving and dose-related risk of crashes after cannabis use. Surveys that established recent use of cannabis by direct measurement of THC in the blood showed that THC positives, particularly at high doses are about 3 to 7 times more likely to be responsible for the crash as compared to drivers with no alcohol or THC in the system. Together…recent use of cannabis may contribute to the crash where past use does not. …similar findings concerning the combined use of alcohol and cannabis in traffic. Combined use of THC and alcohol produced severe impairment of cognitive, psychomotor, and actual driving performance in experimental studies and sharply increased the crash risk. Up to a dose of 300ug/kg THC the risk is found to be equivalent to risk at the legal driving limit for alcohol.

An Economic and Social research Council team led by Dr Philip Terry of Birmingham University released a study on 27th January 2004. Most regular cannabis users admitted to driving under the influence of the drug in spite of being aware that it impairs their performance. 74% had taken a car or motorbike on the road while feeling stoned, 70% believed it had a bad effect on their driving, but 41% felt their actions were acceptable. 100 frequent users (4 to7 times a week) and 90 casual users (no more than 4 days a month) were questioned. One third of the frequent users were willing to drive even when they considered themselves to be "very high". Nearly 80% said roadside testing would be a deterrent although one in eight had been stopped while under its influence and none had been tested for intoxication by the drug or charged for being under its influence.

A bulletin from The New South Wales Bureau of Crime Statistics and Research Number 87 in September 2005 by Jones et al, concluded that "Random drug testing appears to act as a more effective deterrent against drug-driving than an increase in the severity of sanctions or providing factual information about the risks associated and the behaviour".

The Monash University Accident Research Centre in Australia produced a report in 2004 reviewing the epidemiological, driving performance and drug screening literature as it relates to cannabis and road safety. Data for fatally injured drivers between 1997 and 1999 show that 8.5% of those tested were positive for THC, the psychoactive component. They were found to be significantly more culpable than drug-free drivers, even more so when the cannabis was combined with alcohol. They reported, "Recent on-road and simulator studies have set the bench mark for cannabis and driving research. There is no doubt that recent research is continuing to show that cannabis, both alone and with alcohol, impairs a range of measures of driving performance. The predominant form of impairment observed after smoking cannabis alone is an increase in lane-weaving behaviour….also… increased variability in headway to a lead vehicle. This is an

important finding because it is commonly interpreted as reflecting the ability to perceive changes in the relative velocities of other vehicles and ability to adjust own speed accordingly, and is suggestive of impaired perceptual abilities. When cannabis is combined with alcohol, variability of headway is again increased, and variability in lane-weaving behaviour is increased to a greater extent than for cannabis alone. This is again indicative of impaired performance. Furthermore drivers with both cannabis and alcohol take significantly longer to react to changes in the speed of other vehicles. The frequency of visual search for traffic at intersections has been found to be similar for placebo, alcohol alone and cannabis alone, but reduced significantly when alcohol and cannabis are combined. ….drivers are less able to respond to peripheral traffic while maintaining performance on the central driving task".

2005 Asbridge et al looked at adolescent Canadians and cannabis use before driving. 'While the current findings cannot confirm whether DUIC (Driving Under the Influence of Cannabis) was directly responsible for a MVC (Major Vehicle Crashes), adolescents who used cannabis in the one hour prior to driving were more likely to be involved in MVCs. The risk was around double those who didn't use cannabis.

Dr Katherine Papafotiou told a seminar at Swinburne University of Technology, Victoria, Australia on October 13th 2006 that while cannabis manifests itself differently to alcohol, it can be equally dangerous when used before driving. Cannabis users were more likely to lane-weave and stop too close to vehicles in front of them. She also found that driver errors occurred more often when alcohol and cannabis were both present. The 3-year study tested 80 Victorians between 21 and 35 who were either regular or irregular users.

2007, Khiabani HZ et al found that THC affects the cognitive and psychomotor skills of drivers. These effects could last longer than a measurable concentration of THC in the blood. Culpability studies have recently demonstrated an increased risk of becoming responsible in fatal or injurious traffic accidents even with low blood concentrations of THC. It has also been demonstrated that there is a correlation between the degree of impairment, the drug dose and the THC blood concentration.

Another Australian study in August 2007 by Ch'ng and others found that cannabis was the most frequently found drug in the systems of motor vehicle drivers presenting to an adult major trauma centre in Victoria. The blood of 436 victims was analysed, 46.7% contained metabolites of cannabis, 15.6% benzodiazepines, 11% opiates, 4.1% amphetamines, methadone 3% and cocaine 1.4%. THC was found almost exclusively in the 15 to 44 year old age group. "Drug usage found in this group of injured drivers was disturbingly high".

NIDA (National Institute on Drug Abuse) in the USA funded a study on drugs, including alcohol, and driving published in November 2007. In 2006, 30% of high school seniors reported driving after drinking heavily or using drugs, or being a passenger in a car where the driver had been drinking heavily or using drugs, at least once in the previous 2 weeks. Although the numbers reduced between 2001 and 2003, declining from 35 to 31%, after 2004 it had leveled off. In 2006, 13% had driven after using marijuana. Vehicle accidents are the leading cause of death among those aged 15 to 20.

2008 The RAC Foundation reported the results of a survey of more than 2000 users of Facebook. It was looking at texting with a mobile phone while driving. 45% of UK drivers s use SMS (Short message services) while driving. Particularly the young. They commissioned TRL (Transport Research Laboratory) to study the level of impairment caused by texting while driving. TRL driving simulator was used, as it had been previously for alcohol, cannabis and moblile phone conversations. 17 young people between 17 and 24 were used. Reaction times to trigger stimuli were 35% lower when texting, compared with alcohol, 12% lowering and cannabis 21%. Texters did reduce the speed but were more likely to stray into adjacent lanes and the speed slowdown didn't help.

An EMCDDA report on drug use and driving December 2008 found that:
Cannabis can have a detrimental effect on driving ability as it impairs some cognitive and psychomotor skills necessary for driving.
Most of the effects increase in a dose-dependent manner.
Drivers are awareof the impairment but can only partially compensate.
Alcohol with cannabis causes additional impairment.
Chronic use can lead to performance deficiencies that last longer than intoxication and worsen with frequency and length of use.
There is an increased risk of being involved in an accident and this is worsened with the combination with alcohol. Use of either drug alone is less risky.

2008, Ronen and others assessed the effects of 2 (13mg and 17mg) doses of THC relative to alcohol (0.05% BAC) on driving performance, physiological strain, and subjective feelings. 14 healthy students, all recreational cannabis users took part. Both levels of THC cigarettes significantly affected the subjects in a dose-dependent manner. The moderate dose of alcohol and the low THC dose were equally detrimental to some of the driving abilities, with some differences between the 2 drugs. THC primarily caused elevation in physical effort and physical discomfort during the drive while alcohol tended to affect sleepiness levels. After the THC administration subjects drove significantly slower than in the control condition, while after alcohol ingestion, subjects drove significantly faster than the controls. No THC effects were observed after 24 hours on any of the measures.

2010 June 2nd Alan Crancer conducted a study into traffic deaths in California from the use of marijuana. He found that the largest increase in fatalities in fatal crashes where the driver tested positive for marijuana ocurrred over the 5 years following the establishment of the medical marijuana programme in January 2004. There were 1240 fatalities under these circumstances for the 5 years compared to 631 fatalities for the 5 years before, an increase of almost 100%. He suggested that the TC2010 (Regulate, Control and Tax Cannabis Act) initiative might triple the number of marijuana-related deaths on California's highways.

2010 Beirness and Beasley carried out a roadside survey of alcohol and drug use among drivers in British Columbia. 1533 vehicles were selected. 89% of drivers provided a breath sample and 78% a sample of oral fluid. They found: 10.4% tested positive for drugs, 8.1% had been drinking, 15.5% tested positive for alcohol, drugs or both. Cannabis and cocaine were the commonest drugs found.
Conclusions: 'The finding that drug use is more common than alcohol use amomng drivers highlights the need for a unique and separate societal response to the use of drugs by drivers commensurate with the extent of safety risks posed to road users. The observed differences between driving after drug use and driving after drinking have implications for enforcement and prevention'.

The increasing toll of accidents caused by drugged drivers is well publicised in the press. Recent reports include the death of a four-year old girl by a driver who had earlier smoked 2 cannabis joints. Barnaby Pearce 19, driving at almost 80 mph in a 60 mph zone, smashed into the side of a car driven by the girl's grandfather (Daily Mail 19/8/05). Another 19 year old, Mitch Treliving killed himself and 7 other people in a head-on crash after driving at 100mph and losing control. His airborne BMW landed on a Land Rover on the opposite carriageway. A pathologist said there were trace amounts of alcohol in his blood but more significant levels of cannabis (Daily Mail 14/4/05). And David Whitnall 26, a self-confessed user of skunk, almost daily since his teens, ploughed into the back of a Fiat at 120mph while steering his sports car with his knees. He killed a woman and severely injured her husband. He was given 6 years in prison and a 10-year ban. Skunk was found in his possession (Times 3/2/06). The driver of a speedboat that killed a 2 year-old British boy on a beach in the Bahamas in 2002 has tested positive for cannabis. Blood and urine samples were taken at the time but never tested. When a Metropolitan police team tested them much later, the facts came to light. He also was without a proper licence or insurance. James Bain has not yet been prosecuted over the death (Daily Mail 07/01/07). The pilot of a 1946 Piper J3 Cub in Walnut Ridge Little Rock in America was found to have enough marijuana in his system that may have contributed to an accident which killed himself and one passenger
(Associated Press 2007, http://www.todaysthv.com/printfullstory.aspx?storyid=41149).

2011 Li and others looked at mandatory testing and aviation accidents in the USA. 'The odds of accident involvement for employees who tested positive for drugs was almost 3 times the odds for those who tested negative.

2011 June Romano et al found in the US that, of those who died in a crash, about 25% tested positive for drugs. The most common were marijuana and stimulants like cocaine and amphetamines. Of drivers simply randomly pulled over, 14% tested positive. This suggests that drugs do contribute to road deaths as the presence was almost twice as high among those killed. 44,000 fatally injured drivers in the USA were studied between 1998 and 2009. Stimulants were linked to all types of crashes – speeding, ignoring other laws, inattention or not using seatbelts. Marijuana linked with speeding and non belt use.

2011 Mu-Chen and others produced a review paper for vehicle crashes for users of marijuana. 9 epideiologic studies were examined in the past 2 decades. They found that drivers who test positive for marijuana or drive within 3 hours of taking it are more than twice as likely to be involved in a crash than non-users. The greater the amount of marijuana compounds in the urine, also the more frequent self-reported marijuana use were both associated with a greater risk of a vehicle accident. 28% of drivers who

died in an accident and more than 11% of drivers in general, tested positive for non-alcohol drugs, most commonly cannabis.

2012 February SADD (Liberty Mutual Insurance and Students Against Destructive Decisions) commissioned a report into teens driving under the influence of marijuana. Nearly 1 in 5 said they had driven after smoking the drug. Almost 2,300 11th and 12th graders were studied. A growing percentage do not see marijuana as a distraction. More than a third of those who had driven after smoking failed to acknowledge their driving may have been impaired. The figure is higher than those who drove after drinking alcohol (13%).

2012 Ashbridge et al reviewed the literature on vehicle accidents. *Results*. We selected nine studies in the review and meta-analysis. Driving under the influence of cannabis was associated with a significantly increased risk of motor vehicle collisions compared with unimpaired driving. *Conclusions*. Acute cannabis consumption is associated with an increased risk of a motor vehicle crash, especially for fatal collisions. This information could be used as the basis for campaigns against drug impaired driving, developing regional or national policies to control acute drug use while driving, and raising public awareness.

2012 Bosker and others looked at the effects of medicinal THC (Dronabinol)on driving performance. They found that Dronabinol impairs driving performance in occasional and heavy users in a dose-dependent way, but to a lesser degree in heavy users due possibly to tolerance. The Standard Field Sobriety Test is not sensitive enough to clinically relevant driving impairment caused by oral THC.

2013 Bergamaschi et al investigated the effects of cannabis on driving skills. 30 male chronic daily cannabis smokers lived in a secure research unit for up to 33 days. Blood was collected daily. 27 of the 30 were THC positive on admission. Only 1 of 11 participants was negative at 26 days. 2of 5 remained posititive for 30 days. Cannabis is second only to alcohol for causing impaired driving and motor vehicle accidents. For the first time these results show that cannabinoids can be detected in blood of chronic daily cannabis smokers during a month of sustained abstinence. This is consistent with the time course of persisting neurocognitive impairment reorted in recent studies and suggests that establishment of 'per se' THC legislation might achieve a reduction in motor vehicle injuries and death.

2013 Battistella et al Investigated how cannabis smoking affects skills necessary for driving. In conclusion, we have shown that in occasional smokers cannabis globally altered the activity of the main brain networks involved in cognition despite the low THC concentrations. Subjects might be more attracted by intrapersonal stimuli ("self") instead of orienting attention to task performance, and this results in an insufficient allocation of task-oriented resources. Effects on BOLD (Blood Oxygen Level Dependent) response were associated with the subjective evaluation of the state of confusion. By contrast, we failed to find any quantitative correlation between the THC levels measured in whole blood and either the BOLD signal or the psychomotor performance. These results bolster the "zero tolerance policy" that prohibits the presence of any amount of THC in the blood while driving.

2013 June Dupont wrote a paper 'Marijuana Use is a Serious Highway Safety Threat: 5ng/ml Marijuana Impairment Limits Give Drivers a Free Pass to Drive Stoned.

2013 SAM (Smart Approaches to Marijuana, source Dr Fiona Couper, WA state toxicologist) looked at impaired driving trends for Marijuana in Washington State. In 2009-10 the percentage went down to –1.1%. 2010-11 it was +6.3%, 2011-12 –4.6% and 2012-13 it jumped to a huge 50.8%

2013 Li et al invsestigated 737 cases where drivers had been involved in fatal road crashes in 2007 controls (7719) were participants of the 2007National roadside Survey of Alcohol and Drug Use by drivers. 31.9% of the cases and 13.7% of the controls tested positive for at least one non-alcohol drug. The estimated odds ratio (OR) of fatal crash involvement associated with specific drug categories were 1.83 for marijuana, 3.03 for narcotics, 3.57 for stimulants and 4.83 for depressants. Drivers who tested positive for both alcohol and drugs were at substantially heightened risk relative to those using neither alcohol or drugs (OR 23.24).

Mail Online January 16th 2014 Testing for cannabis will begin this year. One in nine 17-24 year olds have admitted driving after taking drugs. Eleven police forces will try the 'SPITALYSER'. Drug users are 50 times less likely to be covicted than drunks. Offenders will get an automatic 12-month ban as well as facing 6months in jail and a £5,000 fine.

2014 Brady and Li discovered a sharp rise in drugged driving fatalities. The rate has tripled for those who tested positive for marijuana. Of 23,591 who were killed within an hour of the crash, 39.7% tested positive for alcohol, and 24.8% for other drugs. For marijuana, rates rose from 4.2% to 12.2% over the period of 1999 to 2010. This substantial increase in the presence of marijuana was found across all groups and both sexes.

2014 Terry-McElrath et al investigated unsafe driving among US High School Seniors. The highest rate of unsafe driving was assocaited with simultaneous use of alcohol and marijuana.

2014 May Whitehill et al found that driving and riding underage is common among marijuana using college students. Past 28 day use of only marijuana was associated with a 6.4 fold increase risk of driving after substance abuse.

2014 July Salomonsen-Sautel and others looked at trends in fatal vehicle crashes before and after marijuana commercialisation in Colorado. In Colorado where medical marijuana has been available since 2009, the trend in positve testing drivers fatally injured in accidents doubled. No increase was seen in states without medical marijuana or people who tested positive for alcohol.

2014 National Transportation Safety Board conducted a survey on pilots and drugs. They found in 2011 that 40% of all pilots killed in non-commercial airplane crashes in recent years have medication in their systems – the most common being antihistamines and heart medications. Illicit drugs were found in nearly 4% of the deceased pilots. This was up from 10% in the 90s. 6,677 killed pilots between 1990 and 2012were looked at. Some 3.8% of deceased pilots tested positive for illegal drugs between 2008 to 2012, up from 2.3% in 1990 to 1997. Marijuana was by far the commonest illicit drug found.

2015 Jan Keyes et al looked at driving fatalities in states of the USA. Alcohol, marijuana or both were involved in half of young driver fatalities from1999-2011. 7,191 fatal accidents involving drivers between 16 to 25 from 9 states, California, Connecticut, Hawaii, Illinois, New Hampshire, New Jersey, Rhode Island, Washington State and West Virginia. More than half the crashes occurred in California. 50.3% had used alcohol, marijuana or both. Of these, 36.8% were under the influence of alcohol, 5.9% marijuana alone and 7.6% had used both substances.

2015 Berning et al of the NHTSA (USA National Highways Traffic Safety Administration) found that drinking and driving is falling, but use of illegal drugs is rising. The number of weekend nighttime drivers with evidence of drugs in their system climbed from 16.3% in 2007 to 20% in 2014. The number of drivers with marijuana in their systems grew by nearly 50%.

2015 May, Pollini et al looked at the effects of marijuana decriminalisation on California drivers. They found a statistically significant increase in the prevalence of cannabinoids among fatally injured drivers in 2012 (17.8%) compared to the pre-decriminalization period 2008-2010 (11.8%) The adjusted odds of testing positive for cannabinoids were also significantly higher in 2012.

2015 May, Woodall et al investigated drug driving in fatal motor vehicle collisions, in Ontario in a one year period. Of the 229 cases included in the study, 56% were positive for alcohol and/or drugs. After alcohol, cannabis was the most frequently encountered substance (27%), followed by benzodiazepines (17%) and antidepressants (17%).

2015 Hartman et al looked at cananbis effects on driving lateral control with and without alcohol. SDLP (Standard Deviation of lateral Position) was measured. SDLP was a sensitive cannabis-related lateral control impairment measure. Driving during blood THC 8.2ug/L increased SDLP similar to notably-impairing alcohol concentrations. Concurrent alcohol and cannabis produced additive rather than synergystic effects.

2015 GHSA (Governors Highway safety Association) in the USA has just reported on drug driving. Drivers are almost as likely to be under the influence of marijuana or prescription drugs as alcohol. Drunk driving is declining as drug driving shows a steady increase. Data from fatal crashes suggests that nearly 40% of victims tested had had drugs in their system, a third testing positive for marijuana.

2015 Ewing and others looked at early substance use and subsequent DUI in adolescents. At age 12, adolescents with more positive beliefs about cannabis and more ability to resist marijuana offers, had significantly higher risk of DUI/RWDD(Riding with Drinking Driver) 4 years later. At 14, youth with

more past month alcohol use, positive beliefs re marijuana, exposure to peer AM (Alcohol and Marijuana) use and family marijuana use, had a higher risk of DUI/RWDD at age 16.

2015 (October) Washington Traffic Safety Commission Report:
In 2014, 84.3% of drivers, testing +ve for cannabinoids were +ve for THC compared with 44% in 2010. Among the 75 drivers involved in fatal crashes testing +ve for THC, approximately half (38) exceeded the 5ng/ml THC per se limit. The frequency of drivers, +ve for THC alone or in combination with other drugs/alcohol (75 drivers) was highest in 2014 compared with the previous 4-year average of 36. Among drivers in fatal crashes testing for only THC or carboxy-THC, the largest proportion are aged 16-25, and the crashes occurred mostly in daytime and on urban roads (58.9%). Over 70% were in multiple-unit fatal crashes. The most frequently reported driver error among drivers with only THC was lane deviation (12.5%) and overcorrecting (8.9%). Most alcohol related fatal crashes are due to speeding.

2016 NPCC (National Police Chief's Council) ran a 'Getting drugs off our roads' Christmas drink and drug drive campaign. The campaign ran from 1st to 31st December 2015 and saw 1888 drug screening devices administered by officers. Nearly 50% of those stopped were found to be under the influence of drugs. More people were detected in December than in the whole of 20i4.

2016 Brubacher et al looked at the prevalence of alcohol and drug use in injured British Columbia drivers**.** Results '1097 drivers met inclusion criteria. 60% were aged 20–50 years, 63.2% were male and 29.0% were admitted to hospital. Cannabis was the second most common recreational drug after alcohol: cannabis metabolites were present in 12.6% (10.7% to 14.7%) of drivers and we detected Δ-9-tetrahydrocannabinol (Δ-9-THC) in 7.3% (5.9% to 9.0%), indicating recent use. Males and drivers aged under 30 years were most likely to use cannabis'.

2016 Radio 5 Live obtained figures from 35 of the 43 police forces in England on arrests for drug driving last year (March 2015 when new laws came in – April 2016). There were almost 8000 arrests. The Metropolitan Police made most arrests – 1636, Greater Manchester Police 5773 and Cheshire 561. South Yorkshire Police drug driving-related arrests went from 13 in the year until the test was introduced to 456 the following year - a 3,400% increase, according to a BBC Yorkshire Freedom of Information (FOI) request.

2016 AAA (American Automobile Association)looked into road deaths in Washington State where recreational use of marijuana is now legal. The number of fatal road crashes has more than doubled since legalisation of cannabis in 2012. In 2014, the number of people killed in crashes where the driver had recently taken pot rose from 50 to 115. Over the same period the number of road deaths rose from 438 to 462. An estimated 1 in 6fatal crashes in Washington involved a driver who had recently used pot. Several states allow a driver to get behind the wheel if they are below a pre-set cannabis limit.

2017 Wettlaufer et al estimated the harms and costs of cannabis-attributable collisions in the Canadian provinces. Cannabis-attributable traffic collisions caused 75 deaths, 4407 injuries, and 24,879 people involved in property damage only collisions in Canada in 2012. This cost $1,094,972,062. costs being higher amongst younger people (16-34).

2017 Chihuri et al looked at the interaction of alcohol and marijuana on fatal road crash risk. 1944 drivers were fatally injured in the USA in 2006,7, and 8. The results were:
'Overall, cases were significantly more likely than controls to test positive for marijuana (12.2% vs. 5.9%, $p < 0.0001$), alcohol (57.8% vs. 7.7%, $p < 0.0001$) and both marijuana and alcohol (8.9% vs. 0.8%, $p < 0.0001$). Compared to drivers testing negative for alcohol and marijuana, the adjusted odds ratios of fatal crash involvement were 16.33 [95% confidence interval (CI): 14.23, 18.75] for those testing positive for alcohol and negative for marijuana, 1.54 (95% CI: 1.16, 2.03) for those testing positive for marijuana and negative for alcohol, and 25.09 (95% CI: 17.97, 35.03) for those testing positive for both alcohol and marijuana'. They concluded that: 'Alcohol use and marijuana use are each associated with significantly increased risks of fatal crash involvement. When alcohol and marijuana are used together, there exists a positive synergistic effect on fatal crash risk on the additive scale'.

2017 Busardo et al looked at neurocognitive correlates in driving under the influence of cannabis. Delta (9)-tetrahydrocannabinol is the main psychoactive compound in cannabis and is commonly identified in blood samples from arrested drivers assumed to drive under the influence of drugs. Changing social norms towards cannabis and higher acceptability towards the drug emphasize the need for comprehensive understanding of the severe neurocognitive and psychomotor effects caused by cannabis and how these

effects are correlated to driving skills and performance. In this review, PubMed, Cochrane Central, Scopus, Web of Science, Science Direct and EMBASE databases were used to identify and select publications up to January 2017 dealing with acute and chronic neurocognitive effects induced by cannabis and ability to drive. Thirty-six s publications were selected for this review. The studies conducted were experimental, using simulators or on-road studies and brain imaging (structural and functional) to better understand the acute and chronic effects on cognitive functions comprised in the short and long-term fitness to drive after cannabis consumption. In a case-crossover self-report study a significant odds ratio increase was found for driving-related injury after combined exposure to cannabis and alcohol compared to cannabis alone (OR of 10.9 and 5.8 respectively). Both experimental and epidemiological studies have revealed that THC affects negatively both, psychomotor skills and cognitive functions. Studies of the acute effects of cannabis on driving have shown that drivers under the influence of this substance are impaired. Indeed, driving under the influence of cannabis doubles or triples the risk of a crash. Specifically, cannabis use impairs critical-tracking tasks increases lane weaving, decreases reaction time, and divided attention.

2017 Malhotra et al looked at the perceptions of NZ drivers on driving under the influence of drugs. 434 drivers completed an online questionnaire. Hallucinogens and opiates were rated as having the greatest driving impairment and cannabis the lowest in illegal drugs. For legal drugs, sedatives were rated highest and anti-nausea and antidepressants the lowest. Drug users rated higher impairment ratings than non-users. Deciding not to drive was, alcohol (73.6%) was greatest, cannabis 57% strong painkillers 42.5%, antidepressants 10.0%. Respondents showed a greater acceptance of driving with legal drugs (43.5) than illicit drugs (10.3%) .

2017 Minaker et al looked at driving among youth, alcohol and marijuana, and passengers in Canada. ‘The 2014-2015 Canadian Student Tobacco, Alcohol and Drug Survey was administered to 24 650 students in provincially generalizable samples A total of 9.1% of grade 11-12 students reported ever driving after drinking, and 9.4% reported ever driving after using marijuana. Almost half (48%) of grade 11-12 students reported ever participating in any risky driving or passenger behaviour. Over one-third (35%) of grade 9-12 students reported ever riding with a driver who had been drinking, and 20% reported ever riding with a driver who had been using marijuana. Boys had higher odds of risky driving behaviours relative to girls, whereas girls had higher odds of risky passenger behaviours relative to boys. Students from rural schools had higher odds of drinking and driving and of riding with a driver who had drunk relative to students from urban schools. There were significant differences in risky driving and passenger behaviours by province.

2017 Li et al assessed individual and joint effects of alcohol andmarijuana on the initiation of fatal two-vehicle crashes. Data on 14,742 culpable drivers (initiators) and 14,742 non-culpable drivers (non-initiators) involved in the same two-vehicle crashes between 1993 and 2014 were obtained from The Fatality Analysis Reporting System. Initiators were significantly more likely than non-initiators to test positive for alcohol (28.3% v 9.6%), marijuana (10.4% v 6.0%), and both substances (4.4% v 1.1%). Relative to those testing negative for both, the OR (Odds Ratio) of fatal crash initiation was 5.37, for those testing positive for alcohol and negative for marijuana 1.62, and for those testing positive for marijuana and negative for alcohol 6.93.

2017 Bonar et al looked at the prevalence and motives for drugged driving among emerging adults presenting to an emergency department. Abstract Emerging adults (N=586) ages 18-25years (54% male, 56% African American, 34% European American) seeking care in an urban emergency department completed past-year surveys of demographics, frequency of DD within 4h of substance use, reasons for DD, and substance use. DD was reported by 24% of participants (with 25% of those engaging in high frequency DD). DD after cannabis use was most common (96%), followed by prescription opioids, sedatives, and stimulants (9%-19%). Common reasons for DD were: needing to go home (67%), not thinking drugs affected driving ability (44%), not having to drive far (33%), and not feeling high (32%). Demographics were not associated with DD, but, as expected, those with DD had riskier substance use.:In this clinical sample, using a conservative measure, DD, particularly following cannabis use, was relatively common among emerging adults.

2017 Arterberry et al looked at empirical profiles of alcohol and marijuana use, drugged driving, and risk perceptions. ‘Latent profile analysis of survey responses from 897 college students were used to identify patterns of substance use and drugged driving. We tested the hypotheses that low perceived danger and low perceived likelihood of negative consequences of drugged driving would identify individuals with higher-risk patterns. Findings from the latent profile analysis indicated that a four-profile model provided the best model fit. Low-level engagers had low rates of substance use and drugged driving. Alcohol-centric engagers had higher rates of alcohol use but low rates of marijuana/simultaneous use and low rates of

driving after substance use. Concurrent engagers had higher rates of marijuana and alcohol use, simultaneous use, and related driving behaviors, but marijuana-centric/simultaneous engagers had the highest rates of marijuana use, co-use, and related driving behaviors. Those with higher perceived danger of driving while high were more likely to be in the low-level, alcohol-centric, or concurrent engagers' profiles; individuals with higher perceived likelihood of consequences of driving while high were more likely to be in the low-level engagers group. Findings suggested that college students' perceived dangerousness of driving after using marijuana had greater influence on drugged driving behaviors than alcohol-related driving risk perceptions'.

2017 Valen et al investigated the increase in cannabis use among arrested drivers in Norway.
A time series observational study of cannabis use among all drivers tested for drugs during 2000-2015 was performed. Descriptive analyses of trends in frequencies and combined use of cannabis with other drugs or alcohol for different age groups and gender were conducted. Tetrahydrocannabinol (THC) is the main psychoactive substance in cannabis and was detected in blood samples from 18,767 suspected drug-impaired drivers. The annual number of THC findings increased during the years 2000-2015 for all age groups. For cannabis-only users, young drivers aged 20-29 years dominated during the whole period, whereas for multidrug-cannabis users the median age increased steadily during 2000-2015. After 2009, the annual increase in THC findings escalated; THC-only findings increased the most'.

2018 GHSA (Governors Highway Safety Association (US) Report Finds 'Drugged Driving' Becoming a Bigger Problem. A new report finds that "drugged driving" is becoming a more pervasive problem on American's roadways, with 44 percent of fatally-injured drivers with known results testing positive for drugs in 2016, up from 28 percent just 10 years prior. On top of that, more than half of those "drugged drivers" had marijuana, opioids, or a combination of the two in their system. Funded by the Foundation for Advancing Alcohol Responsibility, this new report – entitled *Drug-Impaired Driving: Marijuana and Opioids Raise Critical Issues for States* – found that among drug-positive fatally-injured drivers in 2016, 38 percent tested positive for some form of marijuana, 16 percent tested positive for opioids, and 4 percent tested positive for both marijuana and opioids.

2018 Steinemann et al looked at motor vehicle crash fatalities and under- compensated care associated with legalisation of marijuana. Abstract: Half of U.S. states have legalized medical cannabis (marijuana), some allow recreational use. The economic and public health effects of these policies are still being evaluated. We hypothesized that cannabis legalization was associated with an increase in the proportion of motor vehicle crash fatalities involving cannabis-positive drivers, and that cannabis use is associated with high-risk behavior and poor insurance status. Hawaii legalized cannabis in 2000. Fatality Analysis Reporting System (FARS) data were analyzed before (1993-2000) and after (2001-2015) legalization. Presence of cannabis (THC), methamphetamine, and alcohol in fatally injured drivers were compared. Data from the state's highest level trauma center were reviewed for THC status from 1997-2013. State Trauma Registry data from 2011-2015 were reviewed to evaluate association between cannabis, helmet/seatbelt use, and payor mix. THC-positivity among driver fatalities increased since legalization, with a three-fold increase from 1993-2000 to 2001-2015. Methamphetamine, which has remained illegal, and alcohol positivity were not significantly different before versus after 2000. THC-positive fatalities were younger, and more likely single-vehicle accidents, nighttime crashes, and speeding. They were less likely to have used a seatbelt or helmet. THC-positivity among all injured patients tested at our highest level trauma center increased from 11% before to 20% after legalization. From 2011-2015, THC-positive patients were significantly less likely to wear a seatbelt or helmet (33% vs 56%). They were twice as likely to have Medicaid insurance (28% vs 14%). Since legalization of cannabis, THC-positivity among MVC fatalities has tripled statewide, and THC-positivity among patients presenting to the highest level trauma center has doubled. THC-positive patients are less likely to use protective devices and more likely to rely on publically funded medical insurance. These findings have implications nationally and underscore the need for further research and policy development to address the public health effects and the costs of cannabis-related trauma.

2018 Samuel Montfort of The Insurance Institute for Highway Safety produced a report, 'Effect of recreational marijuana sales on police reported crashes in Colorado, Oregon, and Washington'. ABSTRACT In January 2014, Colorado became the first U.S. state to allow retail sales of recreational marijuana, with Washington (July 2014) and Oregon (October 2015) following shortly afterward. With more states weighing legalization, it is important to understand the degree to which recreational marijuana legalization has affected traffic safety outcomes. The current study was based on the 2018 Highway Loss Data Institute research on the subject, which estimated that the legalization of retail sales was associated with a 6.0% increase in insurance collision claims compared with control states. The current study investigated police-reported crashes rather than insurance claims. Crash rates were computed for each

month between January 2012 and December 2016 for the three study states as well as their neighboring states, which served as controls. Controlling for several demographic factors, the change in crash rate that occurred after recreational marijuana was legalized was compared with the change in crash rate in the control states over the same time frame. The legalization of retail sales in Colorado, Washington, and Oregon was associated with a 5.2% higher rate of police-reported crashes compared with neighboring states that did not legalize retail sales. These results contribute to the growing body of research on the impact of recreational marijuana legalization.

2019 Bonar and others found worrying statistics around medical cannabis users operating vehicles. More than half of people who take medical cannabis for chronic pain say they've driven under the influence of cannabis within 2 hours of using it, at least once in the last 6 months. One in five of them said they'd driven while very high in the past 6 months. Nearly 270,000 Americans in Michigan use medical cannabis. "There is a low perceived risk about driving after using marijuana, but we want people to know that they should ideally wait several hours to operate a vehicle after using cannabis, regardless of whether it is for medical use or not," Bonar said. "The safest strategy is to not drive at all on the day you used marijuana." There is uncertainty about how marijuana could affect driving for chronic daily users, who might have even longer-lasting effects that linger in their system, Bonar added. Bonar says that when people drive under the influence of marijuana their reaction time and coordination may be slowed down and they could have a harder time reacting to the unexpected. If they are in a risky situation, they could be more likely to be involved in motor vehicle crash, because they would not be able to respond as quickly.

2019 Vandoros et al looked at the relative risk of motor vehicle collision on cannabis celebration day in Great Britain. Abstract. Cannabis celebration day, also known as "420 day", takes place at 4:20pm on April 20 every year. The objective of this paper is to study whether there is an increase in road traffic collisions in Great Britain on that day. We used daily car crash data resulting in death or injury from all 51 local police forces covering Great Britain over the period 2011–2015. We compared crashes from 4:20pm onwards on April 20 to control days on the same day of the week in the preceding and succeeding two weeks, using panel data econometric models. On the average cannabis celebration day in Britain, there were an additional 23 police-reported collisions compared to control days, corresponding to a 17.9% increase in the relative risk of collision.

2019 Romano et al investigated the use of alcohol and cannabis use among adults driving children in Washington State. Abstract: It is unknown how many drivers are impaired by alcohol or cannabis with children as passengers (a situation known as driving under the influence child endangerment [DUI-CE]). This study examines the prevalence and patterns of alcohol and cannabis use among drivers with children on weekend nights and risk perceptions among these drivers. Data came from 2,056 drivers (1,238 male) who participated in the Washington State Roadside Survey between June 2014 and June 2015. Oral fluid, blood, and breath samples were used to measure cannabis and alcohol use. Self-reported data were used to assess risk perceptions. Descriptive tabulations, weighted prevalence estimates, and chi-square tests were conducted. **Results:** Compared with other drivers, those who drove with a child were more likely to be driving during the daytime (46.6% vs. 36.3%, $p = .03$), less likely to be alcohol positive (0.2% vs. 4.5%, $p < .0001$), but as likely to be positive for Δ-9-tetrahydrocannabinol (THC) (14.1% vs. 17.7%, $p = .29$). Drivers with a child were less likely to report moderate to severe marijuana problems (3.3%) than those without a child (8.4%) ($p < .02$). Most drivers reported that cannabis use was very likely to impair driving. Among those who did not perceive any risk, 40.6% of drivers with a child and 28.9% of drivers without a child tested positive for THC. **Conclusions:** Although most drivers with children did not drink and drive, many tested positive for cannabis, although it is unclear how many drivers may have been impaired. There is a need to examine driving situations that may put children at risks beyond those related to alcohol.

2020 AAA Since 2012, nearly one in five (18%) drivers involved in fatal crashes were positive for THC. After legalization, the average number of THC-positive drivers involved in a fatal crash jumped from 56 per year to 130. AAA believes the increase raises important traffic safety concerns for drivers across the country because recreational marijuana use is now legal in 11 states and Washington, D.C.

2020 Dahlgren et al investigated how recreational cannabis use impairs driving performance in the absence of acute intoxication. Abstract: BACKGROUND: Across the nation, growing numbers of individuals are exploring the use of cannabis for medical or recreational purposes, and the proportion of cannabis-positive drivers involved in fatal crashes increased from 8 percent in 2013 to 17 percent in 2014, raising concerns

about the impact of cannabis use on driving. Previous studies have demonstrated that cannabis use is associated with impaired driving performance, but thus far, research has primarily focused on the effects of acute intoxication. METHODS:The current study assessed the potential impact of cannabis use on driving performance using a customized driving simulator in non-intoxicated, heavy, recreational cannabis users and healthy controls (HCs) without a history of cannabis use.RESULTS: Overall, cannabis users demonstrated impaired driving relative to HC participants with increased accidents, speed, and lateral movement, and reduced rule-following. Interestingly, however, when cannabis users were divided into groups based on age of onset of regular cannabis use, significant driving impairment was detected and completely localized to those with early onset (onset before age 16) relative to the late onset group (onset ≥16 years old). Further, covariate analyses suggest that impulsivity had a significant impact on performance differences. CONCLUSIONS:Chronic, heavy, recreational cannabis use was associated with worse driving performance in non-intoxicated drivers, and earlier onset of use was associated with greater impairment. These results may be related to other factors associated with early exposure such as increased impulsivity.

2020 Colorado Department of Transportation reported on cannabis and serious vehicle crashes. Executive Summary: Colorado continues to see cannabisinvolved traffic crashes that result in serious consequences. Ongoing education and outreach campaigns in recent years have successfully raised awareness that driving under the influence of cannabis is illegal, but studies show behavior is not changing, and motorists are continuing to drive after consuming cannabis. In 2017, the Colorado Department of Transportation (CDOT) launched The Cannabis Conversation, a two-year, statewide campaign to learn about Coloradans' opinions regarding driving under the influence of cannabis (DUIC). This report summarizes what CDOT has learned from the campaign, which engaged with tens of thousands of people throughout Colorado. 1. People who consume cannabis more often consider driving under the influence of marijuana to be less dangerous. 2. Many cannabis users are highly skeptical of the laws, policies and enforcement regarding driving under the influence of cannabis — and want credible, nuanced information. 3. The key to reaching some skeptics is to lead with feelings and follow with facts.

2020 Kamer et al looked at change in traffic fatality rates in the first 4 states to legalise recreational marijuana. Marijuana use impairs driving, but researchers have not yet conclusively determined if a state's legalizing recreational marijuana is associated with traffic fatality rates. Two early studies reported no significant change in roadway deaths following legalization in Colorado and Washington, whereas a study including Oregon reported a temporary increase. A more recent study, including 2017 data, found a statistically significant increase in fatal crashes only after commercial stores opened, suggesting that the effect of legalization may take more time to observe.

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Cancer and the Respiratory System

There are several problems associated with the investigation of possible links between cannabis use and any carcinogenic effects it may have on human cells.

There are now some 140,000 or so scientific research papers on tobacco, while those on cannabis still amount only to about a tenth of that number. It is a relatively young science and, like tobacco, its side effects are usually not apparent for decades.

Cannabis smoking has only been widespread in Western society since the early 1970s and there would presumably be a 20 to 30 year latency period between the initiation of smoking and the development of cancer as is the case with tobacco.

Cannabis smokers often mix tobacco with their cannabis so they run all the well-documented risks of developing cancer associated with tobacco smoke. Relatively few of them smoke cannabis alone so any consequences and therefore causes are almost impossible to separate out. Marijuana smokers are more likely to under report their smoking, if they report it at all.

Large samples are required for case-control studies to take place. It is very difficult to get reliable information about an illegal substance from a large number of people. Questions about cannabis smoking are rarely asked of lung cancer patients.

On the other hand the similarities between tobacco and cannabis are many, the main difference being the presence of nicotine in tobacco and the 60 or so cannabinoids in cannabis (Hoffman et al 1975, Tashkin et al 1997, BMA 1997). So similar side effects may be expected.

Although the number of cannabis "cigarettes" consumed in a day would generally be much fewer than the daily total of tobacco cigarettes, the technique is different. Cannabis smoke is usually inhaled more deeply, held in the lungs for longer and smoked right down to the butt to get full money value. Cannabis cigarettes generally lack filters. (Wu et al 1988). More tar is inhaled from the cannabis butt than from its tip (Tashkin et al 1999).

Cannabis smoke contains 4 to 5 times as much tar as tobacco smoke so the amount of tar deposited in the lungs daily in a cannabis smoker is comparable to that of a tobacco smoker with a 20 a day habit (Benson et al, 1995).

Also the tar from cannabis contains 50% more of some of the carcinogens found in tobacco, notably benzpyrene, a potent carcinogen and a key factor in the promotion of lung cancer (Hoffman et al 1997, Tashkin et al 1997, Novotny et al 1976, Leuchtenberger et al 1983).

For lung cells to become cancerous, a particular combination of cell-growth regulating genes (oncogenes) must become activated or undergo mutation (suppressor genes of tumours).

Marijuana smoke has been reported to produce chromosome aberrations in bacteria as demonstrated by the Ames test (Busch et al 1979 and Wehner et al 1980).

Biopsies of bronchial mucosa have yielded interesting results. Abnormal proliferation of cells (goblet and reserve), transformation of normal ciliated cells to squamous metaplasia (skin-like cells), accumulation of inflammatory cells and abnormal cell nuclei have all been observed (Gong et al 1987, Fliegel et al 1997, Barsky et al 1998). A much higher proportion of these abnormalities was seen in marijuana smokers compared to non-smokers, the number was similar to that of tobacco smokers. Smokers of both tobacco and marijuana exhibited the highest number of all, suggesting the two have an additive effect. Precursors of the development of lung cancer in tobacco smokers include squamous metaplasia and abnormal nuclei (Auerbachet al 1961). Confirmation of these observations also came in 1980 from FS Tennant when he examined US servicemen who were heavy hashish smokers. The mutagenic properties of cannabis smoke were previously recorded in papers in the seventies (Magus and Harris 1971 and Hoffman et al 1975). Human lung explants, exposed to marijuana smoke resulted in DNA and chromosomal alterations (Van Hoozen et al 1997).

Oncogenes and tumour suppressive genes, when mutated, produce proteins which cause cells to multiply rapidly and uncontrollably, resulting in tumours. Two of these proteins were found to be markedly

increased in cannabis smokers compared to tobacco or non-smokers, the effects of tobacco and cannabis being additive (Roth et al 1998).
The mutagenic effects of marijuana smoke have also been observed by Chiesara and Rizzi 1983, Gilmore et al 1971, Herha and Obe 1974 and Stenchever et al 1974.

Benzpyrene can cause alteration of a gene, P53, one of the commonest tumour suppressor genes if acted on by a chemical particle, CYP1A1. THC has been shown to increase production of this particle so making possible the development of respiratory cancer. P53 is thought to play a part in 75% of lung cancers and it is expressed in 11% of cannabis and tobacco smokers (Dinissenko et al 1996, Marques-Magallanes et al 1997).

The immune system has a role to play in the development of cancer. Alveolar macrophages protect the lungs from infection, they also kill tumour cells. Marijuana and tobacco smokers produce two or three times as many of these cells as non-smokers. The effects of smoking both being additive (Barbers et al 1987). The macrophages in both tobacco and marijuana smokers were larger and had more inclusions, probably due to the ingestion of smoke particles (Beals et al 1989). A more recent paper by Baldwin et al in 1997 found significant impairment of the macrophage cells of both tobacco and marijuana smokers. These cells have been shown to have cannabis receptors (Bouaboula et al 1993). Anti-tumour immunity depends on antigen-presenting dendritic cells being able to stimulate the proliferation of T lymphocytes that identify and destroy tumour cells. In in-vitro studies in which dendritic cells and T lymphocytes were incubated with or without THC, the THC suppressed the T cell proliferation in a dose-dependent manner (Roth et al 1997). Two earlier papers on this subject were written in 1975, Peterson et al and Nahas et al. DNA alterations have been seen in the lymphocytes of pregnant marijuana smokers and their newborns. This study is particularly important as tobacco smokers were excluded (Ammenheuser et al 1998). Cannabis smoking also depressed pro-inflammatory cytokine production. Cytokines regulate macrophage function so this may account for the impairment of their ability to kill tumour cells (Baldwin et al 1997).

Experiments on animals have yielded confirmatory evidence for many of the previous observations. In 1979 Rosenkranz and Fleischman found changes in the bronchial epithelia of rats after they had inhaled marijuana smoke for several months. These changes were consistent with precancerous alterations in cells. In the same year Fried and Charlebois administered cannabis smoke to rats during pregnancy and discovered impaired development in the F2 generation, so not only was damage caused to the first but also the second generation. In 1997 Zhu and others treated mice for 2 weeks with THC prior to the implantation of Lewis lung cancer cells. Larger faster-growing tumours resulted suggesting that the THC impairs the development of anti-tumour immunity in vivo. Dubinett et al in 2000 also found that mice injected with THC had reduced capability to fight the growth of tumours.

Painting tar from marijuana smoke on the skins of mice produced lesions correlated with malignancies (Cottrell 1973).

There are a significant number of reports of human cancers that may be linked to the smoking of marijuana. FM Taylor in 1988 examined adults with upper respiratory tract cancer over a period of 4 years. Of 6 men and 4 women, average age 33.5 years, nine had carcinomas of the lungs tongue or larynx, five were heavy cannabis smokers, two smoked it regularly, one had possibly used other drugs and two were non cannabis smokers. It was complicated by the fact that six were heavy alcohol users and six were smokers of tobacco. He concluded that regular marijuana use was a potent factor especially in the presence of other risk factors. He conceded that alcohol and tobacco may have played a part, but pointed out that the peak incidence for cancers due to tobacco or alcohol is in the seventh decade of life. All of these victims were much younger.

In 1989 Caplan and Brigham reported two cases of tongue cancer. One was a man of 37 the other a man of 52. Both were heavy cannabis users, neither smoked tobacco or drank alcohol. Endicott and Skipper in 1991 conducted a 2-centre USA retrospective study. Twenty-six patients of age 41 or less were diagnosed with throat or head tumours. The normal average age for tumours of this type is 57. All 26 were current or former marijuana smokers.

PJ Donald in 1993 examined patients with cancer of the head and throat over a 20-year period. He found 22 patients of age 40 or under on diagnosis, with squamous cell cancer. Their average age was 26. Nineteen of them were cannabis smokers, 16 being heavy users. In 13 the tumour was in the tongue or elsewhere in the oral cavity. Only half of them smoked tobacco.

110 private patients with lung cancer were studied. Nineteen (17%) of them were under 45. Thirteen of these had smoked marijuana of whom 12 reported current tobacco use.
No tobacco-only smoking patients under 45 were noted (Sridhar et al 1994).

An epidemiological study to examine a possible association between cancer and marijuana was published in 1997 by Sidney and colleagues. 65,000 health plan members aged between 15 and 49 in 1979 to 1985 were followed for the development of new cancers till 1993. 182 tobacco-related cancers were detected, of which 97 were in the lungs. The study revealed no risk factors for cancers for lifetime or current use of marijuana.
The major limitation in this exercise is that those who were heavy or long-term users of cannabis were not followed up for long enough to detect cancers. Another criticism is that there may not have been sufficient of these long-term or heavy users to make the study effective. It must be remembered that most marijuana users quit before the level of exposure is sufficient to initiate the development of cancer and cannabis smoking has only been widespread in the USA since the 70s.

Zhang et al in 1999 studied 173 patients with carcinoma of the head and neck and compared them with 176 cancer-free controls. Age, sex, race, education, alcohol consumption and exposure to cigarette smoke either actively or passively, were all controlled for. Marijuana smoking increased the risk of squamous cell carcinoma of the head or neck, and a further increased risk was suggested with rising doses. Among people who smoked once a day the risk factor was 2.1 times compared with non-smokers, with those using it more than once a day the risk factor rose to 4.9. With patients who smoked cannabis and tobacco the risk was 36 times that for non-smokers.

It was reported in the press in January 2000 that a leading cardio-thoracic surgeon, Mr Alan Kirk of Glasgow's Western Infirmary was treating 12 patients aged 27 to 35 for lung cancer. Ten of them admitted they were regular cannabis smokers. Lung cancer normally develops in much older patients. All of them had also used tobacco but Mr Kirk said he thought it likely that cannabis had accelerated the process. He now routinely asks all his younger lung cancer patients whether they have smoked the drug. He has called for large scientific studies to be done.

The most prominent name and authority on cannabis and diseases of the respiratory system is that of Dr Donald Tashkin. He has researched the topic since the early seventies.

In 1993 he listed the factors suggesting that cannabis smoking may be associated with an increased risk of respiratory tract cancers.

1. Cannabis smoke has 50% more of certain carcinogens than tobacco smoke, especially the highly carcinogenic benz-pyrene.
2. Four times as much tar is produced by a cannabis cigarette than a tobacco one.
3. Experiments on animals have shown that cannabis smoke or tar from it is carcinogenic.
4. Heavy cannabis consumers have significantly higher numbers of cellular changes consistent with the preliminary stages of cancer.
5. There have been several reports of young cannabis-using people exhibiting the development of cancer. Tumours have appeared 10 to 30 years earlier than those who smoked tobacco alone.

In a review paper in 2002 he added that examination of the mucous membranes in long-term smokers suggests that THC weakens the immune defences against tumour cells.

In November 2002 the British Lung Foundation produced a paper "A Smoking Gun? The Impact of Cannabis Smoking on Respiratory Health". One of their recommendations was: " The British Lung Foundation recommends a public health education campaign aimed at young people to ensure that they are fully aware of the increased risk of pulmonary infections and respiratory cancers associated with cannabis smoking".

In September 2003 The Thoracic Society of Australia and New Zealand produced a position paper in The Internal Medicine Journal on the respiratory health effects of cannabis (Taylor and Hall). They also called for a campaign. "Public Health Education should dispel the myth that cannabis smoking is relatively safe by highlighting that the adverse respiratory effects of smoking cannabis are similar to those of smoking tobacco…that the respiratory hazards of smoking cannabis are significant…almost all studies indicate that the effects of cannabis and tobacco smoking are additive and independent".

Gardner and others in 2003 found that a cannabinoid, methanandamide, resulted in an increased rate of tumour growth in murine lung cancer.

The death rate from lung cancer in Maori people is 3 times higher than in non-Maoris. In fact they have the highest lung-cancer death rate in the world. The average age of death is lower, 63 compared to 70 years. There is also a high incidence of tobacco smoking in these people, but equivalent rates are seen in areas of Asia and Europe where fewer succumb to cancer of the lung. A high rate of heavy marijuana use among the Maoris has led scientists to suggest that this may be a contributory factor. Research has shown that cannabis use has reached epidemic proportions and is rising (Harwood et al 2004). The Sydney Morning Herald on July 27th 2006 reported that, of the 142,144 people treated by Australia's drug and alcohol treatment agencies in 2004-2005, 13,666 or almost 10% were Aboriginal or Torres Strait Islanders, amounting to nearly 5 times the proportion of indigenous people in the population. Among these people, 21% of males between 10 and 19 years were treated compared to 11% of other Australian males of the same age. With indigenous 10 to 19 year-old females the figures were 19% compared to 11% of the others. Cannabis was the commonest illicit drug for which treatment was sought.

Sarafian et al in 2005 suggested that THC contributes to DNA damage, inflammation and alterations in apoptosis (programmed cell death) in tracheo-bronchial epithelium and concluded that, " THC delivered as a component of marijuana smoke, may induce a profile of gene expression that contributes to the pulmonary pathology associated with marijuana use".

In June 2005 Roth and Tashkin of UCLA, the two leading authors of many papers linking cannabis and cancer for over 10 years, described an epidemiological study at the meeting of the International Cannabinoid Research Society in Tampa, Florida. This paper has yet to appear on the ICRS website. Tashkin reported that they had failed to substantiate the link. Needless to say the press immediately issued banner headlines like "Marijuana is safer than tobacco". However it has emerged that the study lacked statistical power. Tashkin and Roth explained that they had very few patients smoking more than 6 joints a day, a very mild level of consumption. They said that had they had more moderate and heavy smokers, their outcomes would almost certainly have been different. The study was originally designed to have 3 controls for each cancer case, in reality the ratio was around 0.7. Statistics are powerful but not powerful enough to account for gross flaws in sampling errors and study design.

Tashkin also in June 2005, reviewed the literature on lung injury caused by smoking marijuana. He concluded, "Regular marijuana smoking produces a number of long-term pulmonary consequences including chronic cough and sputum, histopathologic evidence of widespread airway inflammation and injury and immunohistochemical evidence of dysregulated growth of respiratory epithelial cells that may be pre-cursors of cancer…….Habitual use of marijuana is also associated with abnormalities in structure and function of alveolar macrophages including impairment in microbial phagocytosis and killing that is associated with defective production of immunostimulatory cytokines and nitric oxide thereby potentially predisposing to pulmonary infection".

Dr Martha Terris et al, of Georgia's Medical College and the Veterans Affairs Medical Centre Augusta, writing in Urology January 2006 reported that, of 52 men between 44 and 60 with transitional cell bladder cancer, 88.5% had a history of marijuana smoking. Almost 31% were still using the drug. 104 controls were seekers of urological care other than bladder cancer. Tobacco smoking is the major risk for bladder cancer but is only common in the over 60s. Since marijuana metabolites have a half-life in urine about 5 times greater than tobacco metabolites, they warned that, "Marijuana smoking may be an even more potent stimulant of malignant transformation in transitional epithelium than tobacco smoking".

A systematic review of 19 studies into the impact of marijuana smoking on the development of pre-malignant lung changes and lung cancer was carried out by Mehra et al in 2006. Deficiences in the methodology of some of the studies were noted. The conclusion was as follows: " Given the prevalence of marijuana smoking and studies predominantly supporting biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings, physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions".

Other adverse respiratory effects are seen with cannabis smoking. In 2004 Moore et al looked at over 6500 adults aged 20 to 59. Current marijuana use was defined as 100+ lifetime use and at least one day of use in the past month. Self-reported respiratory symptoms included chronic bronchitis, frequent phlegm and wheezing, shortness of breath, pneumonia and chest sounds in the absence of a cold. They concluded that

efforts to reduce and prevent marijuana use may have substantial public health benefits associated with decreased respiratory health problem.

In 2006 the risk of lung cancer and past use of cannabis was studied in Tunisia by Berthiller et al. They found that the odds ratio for the past use of cannabis and lung cancer was 4.1 after adjustment for age, tobacco use and occupational exposures. No clear dose-response relationship was observed between the risk of lung cancer and the intensity or duration of cannabis use. "This study suggests that smoking cannabis may be a risk factor for lung cancer".

Bluhm and others in 2006 found that maternal use of recreational drugs increased the risk of neuroblastoma in offspring. 538 children with the cancer were studied, and compared with 504age-matched controls. They concluded that maternal use of any illicit or recreational drug around pregnancy increased the risk of neuroblastoma in offspring, particularly marijuana use in the first trimester of pregnancy. Evaluation of other recreational drugs was limited by infrequent use.

A systematic review of 34 studies on pulmonary function and respiratory complications was carried out in 2007 by Tetrault et al. The summarized findings are as follows:

Short-term marijuana smoking was associated with improved airway response in 10 of 11 challenge studies (effects assessed immediately or shortly afterwards, 15 mins or I hour). However the results of the other one suggested a reversal of this effect after 1.5 to 2 months of marijuana smoking.
Longer-term marijuana smoking was inconsistently associated with airflow obstruction. Results from pulmonary function tests were worse in marijuana smokers than in controls in 8 of 14 studies.
Longer-term marijuana smoking was associated with an increased risk of various respiratory complications (cough, sputum production, wheezing, dyspnea, pharyngitis, worsening of asthma symptoms) in 14 of 14 studies. The overall quality of studies varied, many failed to control for tobacco smoking and none defined a standardized measure of marijuana dose.

A story in BBC News on 3rd June 2007 reported a case of emphysema in a 37-year- old woman who had smoked cannabis for 20 years when it was diagnosed at the age of 34. She had progressed from 2/day to up to 10/day. Dr Onn Min Kon of St Mary's Hospital London believes her cannabis smoking may be to blame for her condition. He has several other young cannabis-smoking patients who have lungs normally seen in 65 year-olds. The woman said, "If I don't stop smoking I won't be around much longer – there is no cure for emphysema, the holes in my lungs are getting bigger…. There should be adverts showing people like me". Dr Kon is planning a study to compare the lungs of cannabis smokers with those of tobacco-only users., he will use lung-function teats and CT scans.

Marijuana worsens breathing problems in current smokers with chronic obstructive pulmonary disease (COPD) according to a paper presented at The American Thoracic Society 2007 International Conference in May 2007. Among people of 40 and over, tobacco smokers were 2.5 times as likely to develop COPD as non-smokers, while smoking cigarettes and marijuana together the risk rose to 3.5 times. The odds of someone smoking tobacco and cannabis developing *any* respiratory symptoms were 18 times more than a person who used neither. The study involved 648 adults of 18 and over (Tan W 2007).

On March 26th 2007, Dr Sarah Aldington of The Medical Research Institute in Wellington presented a paper to The Thoracic Society conference in Auckland. She said that "Approximately 5% of lung cancer cases in those aged 55 and under may be attributable to cannabis, equating to 15 new cases a year. In 2002 306 people were diagnosed in New Zealand with lung cancer. "The younger someone starts smoking cannabis, the higher the risk of lung cancer", she said. The risk of developing the disease increased by about 8% per year for people whose cumulative exposure equated to smoking one joint a day, about the same as a person with a pack a day tobacco habit.

Aldington et al in Thorax 2007, in a study of 339 subjects, divided into 4 smoking groups, tobacco only, cannabis only, cannabis and tobacco and non-smokers of either substance. They concluded that, "Smoking cannabis was associated with a dose-related impairment of large airways function resulting in airflow obstruction and hyperinflation. In contrast cannabis smoking was seldom associated with macroscopic emphysema. The 1:2.5 to 6 dose equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function is of major public health significance".

A connection between cannabis smoking and emphysema was described in a paper by Beshay and others in October 2007. It concluded, "In case of emphysema in young individuals, marijuana use has to be

considered in the differential diagnosis. The period of marijuana smoking seems to play an important role in the development of lung emphysema. This obviously quite frequent condition in young and so far asymptomatic patients will have medical, financial and ethical impact, as some of these patients may be severely handicapped or even become lung transplant candidates in the future".

In 2008, Moir et al compared marijuana and tobacco smoke. Ammonia was present in mainstream marijuana smoke at up to 20 times that isn tobacco smoke, hydrogen cyanide, NO, NOx, and some aromatic amines were 3 to 5 times greater. Sidestream marijuana smoke had more polycyclic aromatic hydrocarbons (PAHs) than sidesteam tobacco smoke. 'The confirmation of the presence, in both mainstream and sidestream smoke of marijuana cigarettes of known carcinogens and other chemicals implicated in respiratory diseases is important information for public health and communication of the risk related to exposure to such materials'.

Hii et al in January 2008 found that marijuana smokers face rapid lung destruction, approximately 20 years earlier than tobacco smokers. Bullous lung disease (bullae) is a condition where air trapped in the lungs causes an obstruction to breathing and eventual destruction of the lungs. The condition can often go undetected, not showing up on chest x-rays. The average age of marijuana smokers with lung problems is 41 compared with tobacco smokers at 65. One of the authors said, " What is outstanding about this study is the relatively young ages of the lung disease patients, as well as the lack of abnormality on chest x-rays and lung functions in nearly half the patients we teasted. Marijuana is inhaled as extremely hot fumes to the peak inspiration and held for as long as possible before slow exhalation. This predisposes to greater damage to the lungs and makes marijuana smokers more prone to bullous disease as compared to cigarette smokers".

A comparison of the carcinogenic effects of cannabis versus tobacco was carried out in New Zealand by Aldington et al January 2008. They found that the lung cancer risk of one marijuana joint a day equals that of a daily packet of cigarettes. For every one joint/day smoked for a year the risk factor rose 8%. This association was similar to the 7% risk seen for a pack/day for a year of tobacco smoking.

Daling et al in 2009, found an association between marijuana smoking and testicular cancer. 369 men between 18 and 44 with testiciular germ cell tumours were investigated in Washington State. Men who smoked the drug once a week or started long-term when they were adolescents were twice as likely to develop the particularly aggressive form, nonseminoma which accounts for about 40% of all cases. Current marijuana use was linked to a 70% increase for the disease.

Tan WC et al, 2009 (April) found that smoking marijuana and tobacco increases the risk of COPD. People over 40 who used both tobacco and marijuana were almost 3 times more likely to suffer from COPD. The use of marijuana alone was not linked to this increase in risk. It appears that the marijuana may act as a kind of "primer" in the airways, augmenting the effects of tobacco.

June 2009, Singh R et al found that cannabis use increases the risk of cancer. They unearthed "convincing evidence" that cannabis smoke damages DNA in ways that could potentially increase the risk of cancer in humans. They discovered that the smoking of 3 to 4 cannabis cigarettes/day would cause the same degree of damage to bronchial mucus membranes as 20 or more tobacco cigarettes/day. Cannabis smoke, because of its lower combustability compared to tobacco, contains 50% more carcinogenic polycyclic aromatic hydrocarbons than tobacco smoke.

June 2009 The CIC (Carcinogen Identification Committee) of The OEHHA (Office of Environmental Health Hazard Assessment) of the California Environmental Protection Agency, determined that marijuana smoke was clearly shown , through scientifically validated testing , according to generally accepted principles, to cause cancer.

2012 Pletcher looked at the association between marijuana exposure and pulmonary function over 20 years. He concluded that 'occasional and low cumulative marijuana use' (2-3 joints/month) was not associated with adverse effects on pulmonary function', but also that there was increasing evidence of lung trouble among smokers of 20 or more/month. However his research was widely criticised. The comparison was made with a tobacco smoker of 8-9cigarettes/day. They did not compare 2-3/month tobacco users with 2-3/month cannabis smokers, or heavy with heavy. They only looked at limited lung function parameters, FeV1 (Forced expiratory Volume) and FVC (Forced Vital Capacity). No microscopic analysis of tissue was carried out. No other area of potential damage was addressed. Marijuana smokers inhale more deeply than tobacco smokers and hold their breaths longer. This may stretch the lungs so resulting in larger volumes.

How much air you can force out of your lungs was the only measurement taken. Other studies have produced different results and can be read in this chapter:

2012 British Lung Foundation C.E.O. Dame Helena Shovelton said that cannabis smoking poses a 20 times greater risk of lung cancer per cigarette than tobacco smoking. Used by more than a third of young people under 24, but 88% believe it's less dangerous than tobacco. A third said it did not harm health. The average puff on a joint is two thirds longer and held in lungs for 4 times longer. So Cannabis smoker inhales 4 times as much tar and 5 times as much carbon monoxide. With each puff the smoke particles become more concentrated and harmful.

Because cannabis can suppress the immune system, smokers are at risk of respiratory problems: coughing, wheezing, sputum production, acute bronchitis and airway obstruction. Also infective lung conditions, TB and legionaire's disease. As well as pneumothorax – collapsed lung and lung cancer. It is estimated that 5% of lung cancers in those aged 55or under may be caused by smoking cannabis.

2012 Sept Lacson et al, Looked at the possible increase of testicular cancer in marijuana users. Testicular cancer is the commonest cancer diagnosed in young men of 15-45 and is increasing. The self-reported recreational use among 163 young men with diagnosed testicular cancer and compared it with 292 healthy controls. Men with a history of marijana use were twice as likely to have sub-types of testicular cancer called non-seminoma, and mixed germ cell tumours. These tumours carry a worse prognosis than the seminoma type.

2014 Chinnappa and others investigated emphysema in North Wales. Eight patients (aged 35-48) In an emergency department for exacerbation of COPD were found to have precocious COPD associated with high cannabis use. All had signs of advanced emphysema. All had at least 10-20 years smoking more than 5 joints/day. Four required long-term oxygen therapy, one is actively listed for a lung transplant. This was all independent of genetic susceptibility. They concluded that the addition of cannabis to tobacco, and high usage at a young age, is leading to an increase of COPD in general and bullous emphysema as a phenotype in particular.

2015 Macleod et al looked at cannabis smoking and its effects on the lungs. Participants consisted of 500 individuals, 242 of them males. The mean age of tobacco-only smokers was 45 and median tobacco exposure 25 pack years. The mean age of cannabis and tobacco smokers was 37 years, median tobacco exposure 19 years rising to 22.5 when tobacco smoked with cannabis. Although tobacco and cannabis use were associated with increased reporting of respiratory symptoms, this was higher in those who also smoked cannabis. Each additional joint year of cannabis use was associated with a 0.3% increase in (COPD) Coronary Obstructive Pulmonary Disease. They concluded that, 'In adults who predominantly smoked resin cannabis mixed with tobacco, additional adverse effects were observed on respiratory health relating to cannabis use'.

2015 Hancox et al Looked at the effects of quitting cannabis on respiratory symptoms.

Associations between changes in cannabis use and respiratory symptoms in a population-based cohort of 1037 young adults (Dunedin Study) were assessed. Participants were asked about cannabis and tobacco use at ages 18, 21, 26, 32 and 38 years. Symptoms of morning cough, sputum production, wheeze, dyspnoea on exertion and asthma diagnoses were ascertained at the same ages. Reducing or quitting cannabis use was associated with reductions in the prevalence of cough, sputum and wheeze to levels similar to nonusers. Frequent cannabis use is associated with symptoms of bronchitis in young adults. Reducing cannabis use often leads to a resolution of these symptoms.

2015 Dr Lisa Charles, Medical Director Victoria Hospital, Castries, St Lucia said that mixing marijuana and tobacco is a dangerous practice and is turning people into 'respiratory cripples'. Over the last 10 years she has seen an increasing epidemic of young people suffering from COPD (Chronic Obstructive Pulmonary Disease). Young people in their 30s have end-stage lung disease. COPD is irreversible and progressive. Patients are literally confined to bed with oxygen cylinders and need full care. Bed space was severely compromised. The cost of treatment is horrendous. The Pan American Health Organisation has said theat COPD is a leading cause of morbidity and mortakity in the Americasand it is both preventable and treatable.

2015 American Lung Association (March 2015). Marijuana smoke has been shown to contain many of the same toxins, irritants and carcinogens as tobacco smoke. The smoke is inhaled more deeply and held in the

lungs for longer. Second hand marijuana smoke contains many of the same toxins and carcinogens found in inhaled smoke, in similar amounts, if not more! Children in the home may be at risk. It causes chronic bronchitis and injures the cell linings of the large airways possibly explaining chronic cough, phlegm productions and wheezing. An immune-compromised person is more susceptible to lung infections (immune system is impaired).

In 1981 the WHO report on cannabis use said, "It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, "risk factors" have been freely identified, although full causality has not yet been established. Nevertheless such risk factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is often not applied to cannabis"… "To provide rigid proof of causality in such investigations is logically and theoretically impossible, and to demand it is unreasonable".

2016 Wilson et al found that 1 in 6 children hospitalized (Colorado hospital) for lung inflammation (coughing, wheezing and other symptoms of bronchiolitis) tested positive for marijuana exposure. More of the children were positive for THC after legalisation (21% compared with 10% before). Secondhand smoke may be a rising child health concern.

2016 Martinasek et al undertook a systematic review of the respiratory effects of inhalational marijuana. Forty-eight articles were collected and categorized by respiratory effects. In particular, lung cancer, bullous emphysema/COPD, and other respiratory symptoms were the primary categories. The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous pneumothorax, bullous emphysema, or COPD. A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation, and other symptoms

2017 Mishra et al looked at cannabis-induced bullous lung disease leading to pneumothorax. 'A 30-year-old man with spontaneous pneumothorax associated with marijuana use was admitted. The patient had no medical conditions and presented to the emergency room with chest pain. The physical examination revealed decreased breath sound on the right side of the chest. Bed side ultrasound of chest showed stratosphere sign, absent lung sliding; consistent with right-sided pneumothorax. The patient underwent placement of a chest tube. Computed tomography chest scans performed on day two also showed bullous lung disease in the right lung. Serial x-rays of the chest showed re-expansion of the lung. Despite the beneficial effects of Marijuana there are deleterious effects which are emphasized here. This case highlights the need for further studies to establish the relationship between marijuana use and lung diseases in the absence of nicotine use'.

2018 Livne et al looked at DSM-5 cannabis withdrawal syndrome Abstract: Cannabis withdrawal syndrome (CWS) was newly added to the Diagnostic and Statistical Manual of Mental Disorders in its most recent edition, DSM-5. With cannabis use increasing among U.S. adults, information is needed about the prevalence and correlates of DSM-5 CWS in the general population. This study presents nationally representative findings on the prevalence, sociodemographic and clinical correlates of DSM-5 CWS among U.S. adults. Participants ≥18 years were interviewed in the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) in 2012-2013. Among the sub-sample of frequent cannabis users in the prior 12 months (≥3 times a week; N = 1527), the prevalence and demographic and clinical correlates of DSM-5 CWS were examined. In frequent cannabis users, the prevalence of CWS was 12.1%. The most common withdrawal symptoms among those with CWS were nervousness/anxiety (76.3%), hostility (71.9%), sleep difficulty (68.2%) and depressed mood (58.9%). CWS was associated with significant disability ($p < 0.001$), and with mood disorders (adjusted odds ratios [aOR] = 1.9–2.6), anxiety disorders (aOR = 2.4–2.5), personality disorders (aOR = 1.7–2.2) and family history of depression (aOR = 2.5) but not personal history of other substance use disorders or family history of substance use problems. CWS is highly comorbid and disabling. Its shared symptoms with depressive and anxiety disorders call for clinician awareness of CWS and the factors associated with it to promote more effective treatment among frequent cannabis users.

2018 Wilson et al found second-hand smoke in kids' lungs. The impact of secondhand marijuana smoke exposure on children is unknown. New methods allow for the detection of marijuana smoke exposure in children. **Abstract:** We studied children who were hospitalized in Colorado and had a parent participating in a smoking cessation study; all children had urine samples remaining from the original study as well as consent for future research. Parents completed a survey and urine samples were analyzed for cotinine and marijuana metabolites, including 11-hydroxy- Δ 9-tetrahydrocannabinol (COOH-THC), by using liquid

chromatography-tandem mass spectrometry. The median age of the children was 6.0 years (range 0–17 years); 57% were boys. Half (55%) were white, 12% were African American, and 33% were of another race; 39% identified as Hispanic. Approximately 46% had detectable COOH-THC, and 11% had detectable THC. Of those with detectable THC, 3 were teenagers, and 6 were <8 years of age. There were no significant differences in urinary COOH-THC concentrations by age, sex, race and/or ethnicity, or socioeconomic status. Children with positive results for COOH-THC were more likely to have parents who use marijuana daily, smoke marijuana versus other forms of use, use daily in the home, and smoke marijuana in another room if the children are around compared with smoking outside. Approximately half of the children who qualified for our study had biological evidence of exposure to marijuana. Researchers in studies such as this provide valuable data on secondhand exposure to children from parents using tobacco and marijuana and can inform public health policies to reduce harm.

2019 Winhusen et al found that cannabis use, with or without tobacco co-use, is associated with respiratory disease. Abstract: Cannabis use is a potential risk factor for respiratory disease but its role apart from tobacco use is unclear. We evaluated the association between regular cannabis use, with and without tobacco co-use, and onset of asthma, chronic obstructive pulmonary disease (COPD), and pneumonia. METHODS: Analysis of a limited data set obtained through IBM Watson Health Explorys, an electronic-health-record-integration platform. Matched controls using Mahalanobis distance within propensity score calipers were defined for: 1) cannabis-using patients (n = 8932); and subgroups of cannabis-using patients: 2) with an encounter diagnosis for tobacco use disorder (TUD; n = 4678); and 3) without a TUD diagnosis (non-TUD; n = 4254). Patients had at least: one recorded blood pressure measurement and one blood chemistry lab result in the MetroHealth System (Cleveland, Ohio). Cannabis-using patients had an encounter diagnosis of cannabis abuse/dependence and/or ≥2 cannabis-positive urine drug screens (UDSs). Control patients, not having cannabis-related diagnoses or cannabis-positive UDSs, were matched to the cannabis-using patients on demographics, residential zip code median income, body mass index, and, for the total sample, TUD-status. RESULTS: Regular cannabis use was significantly associated with greater risk for asthma (odds ratio (OR) = 1.44; adjusted odds ratio (aOR) = 1.50; OR = 1.32), COPD (OR = 1.56; aOR = 1.44; OR = 2.17), and pneumonia (OR = 1.80; OR = 1.84; OR = 2.13) in the total sample and TUD and non-TUD subgroups, respectively. TUD-patients had the greatest prevalence of respiratory disease, regardless of cannabis-use indication. CONCLUSIONS: Regular cannabis use is associated with significantly greater risk of respiratory disease regardless of TUD status. Future research to understand the impact of cannabis use on respiratory health is warranted.

2020 Gracie and Hancox looked at Cannabis use disorder and the lungs. Abstract Cannabis is one of the world's most widely used recreational drugs and the second most commonly smoked substance. Research on cannabis and the lungs has been limited by its illegal status, the variability in strength and size of cannabis cigarettes (joints), and the fact that most cannabis users also smoke tobacco, making the effects difficult to separate. Despite these difficulties, the available evidence indicates that smoking cannabis causes bronchitis and is associated with changes in lung function. The pattern of effects is surprisingly different from that of tobacco. Whereas smoking cannabis appears to increase the risk of severe bronchitis at quite low exposure, there is no convincing evidence that this leads to chronic obstructive pulmonary disease. Instead, cannabis use is associated with increased central airway resistance, lung hyperinflation and higher vital capacity with little evidence of airflow obstruction or impairment of gas transfer. There are numerous reports of severe bullous lung disease and pneumothorax among heavy cannabis users, but convincing epidemiological data of an increased risk of emphysema or alveolar destruction are lacking. An association between cannabis and lung cancer remains unproven, with studies providing conflicting findings.

2020 Sack et al looked at allergic and respiratory symptoms in employees of indoor *Cannabis* Grow Facilities. Background: While little is known about the occupational hazards associated with *Cannabis* cultivation, both historical research in the hemp industry and preliminary data from modern grow houses, suggest that *Cannabis* workers may be at increased risk of respiratory and allergic diseases.
Objectives We sought to investigate the association between workplace exposures and health symptoms in an indoor *Cannabis* grow facility in Washington State, USA.
Methods We performed a cross-sectional study with all consenting employees in an indoor *Cannabis* grow facility in Seattle, WA using a questionnaire. The questionnaire gathered data on respiratory, ocular, nasal, and dermal symptoms. A subset of employees with work-related symptoms underwent repeated cross-shift and cross-week measurement of spirometry, fractional exhaled nitrogen oxide (FeNO), and skin prick testing for *Cannabis* sensitization. Exposure to *Cannabis* dust was classified based on self-described tasks, expert opinion, and exposure monitoring of particulate matter. Multivariable logistic regression was undertaken to examine associations between exposure to *Cannabis* dust (classified

as low, medium, and high) and health symptoms. Linear mixed effects models examined the relationship between cross-shift and cross-week changes in spirometry and FeNO.
Results Ninety-seven percent (97%) of the employees (n = 31) surveyed were recreational cannabis users, with 81% (n = 25) smoking cannabis multiple times per day. Twenty-two (71%) employees reported one or more work-related symptoms: 65% respiratory, 39% ocular, 32% nasal, and 26% dermal symptoms. There was a trend toward increased likelihood of work-related symptoms with increasing exposure to *Cannabis* dust, although none of these results were statistically significant. Of the 10 employees with work-aggravated symptoms, 5 had borderline-high or high FeNO, 7 had abnormal spirometry, and 5 had evidence of *Cannabis* sensitization on skin prick testing. FeNO increased by 3.78 ppb (95% confidence interval 0.68–6.88 ppb) across the work-week and there was a trend toward cross-week and cross-shift reduced airflow. **Conclusions** We found a high prevalence of work-related allergic- and particularly respiratory symptoms in the employees of one indoor *Cannabis* grow facility in Washington State. A high proportion of employees with work-aggravated symptoms had findings consistent with probable work-related asthma based on high FeNO, airflow obstruction on spirometry, and *Cannabis* sensitization on skin prick testing. However, due to the high incidence of recreational cannabis use among these workers, the relative influence of occupational versus recreational exposure to *Cannabis* dust on the respiratory health and sensitization status of these workers could not be resolved in this study.

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Cannabis and Dependence

Drug abuse: Individuals cause harm to themselves (physical, mental or social) or to others through use of the drug. There is a degree of control, use is not constant and they can abstain.

Dependence: A compulsive need for the drug. All harm (physical, mental and social) is ignored as are all other everyday interests. Obtaining the drug becomes all-consuming.

Physical dependence: produces tolerance where more of the drug is needed to get the same effect. Changes take place in the brain. Also observed are **withdrawal symptoms** when use of the drug is stopped. (Because of the long-term persistence of THC in brain cells, the withdrawal symptoms are ameliorated unlike the more dramatic symptoms of heroin withdrawal which is metabolised quickly. Heroin users need a "fix" about every 4 hours).

Psychological dependence: A strong desire or craving for the drug. The drugged state is preferred to normality. It is the more difficult to treat.

Almost all addictive drugs stimulate a part of the brain, the mesolymbic **dopamine system** which is the Central nervous System's Reward Pathway. Cannabis receptors are found here. When stimulated, these receptors begin the cycle of reward which can lead people on to take more. This circuit is shared with animals. (Koob GF 1992).

Some early experiments on dependence failed to prove anything as the doses given to experimental subjects were unrealistically low and the timescale was too short (e.g. Hollister 1986).
However in 1983, Jones et al had given higher and more frequent doses for 3 weeks. Their subjects rapidly developed tolerance and showed withdrawal symptoms. And before that, in 1979 Georgotas and Zeidenberg gave daily doses of 210mg THC, equivalent to a single 1g cigarette today. After 4 weeks the subjects found the marijuana "much weaker" In the first week of abstinence they were irritable, unco-operative, resistant and "hostile", suffered from insomnia and were hungry. The symptoms took 3 weeks to disappear.

After 1986, a substantial number of studies and observations have supported these findings, ie that dependence develops in association with long-term use. (e.g. Miller and Gold 1989, Gable 1993 and Stephens et al 1993).

It was also generally agreed that tolerance develops (Compton et al 1990, Oviedo et al 1993, De Fonseca et al 1994).
Haney et al 1999, researching oral cannabis, THC and cigarettes with 1.8-3.1% THC, described in particular the tolerance to the "high" sought by users.
This tolerance results in a rise in dosage or increased use observed in experiments and in studies of users (Swift et al 2001, Coffey et al 2000, Von Sydow et al 2001)
Compton also described the withdrawal symptoms he found: sleeplessness, anxiety, irritability, sweating, trembling, nausea and weight loss. The severity of these symptoms increased with a longer time, a greater frequency and a larger dosage.

Withdrawal symptoms were also found by Duffy and Milin 1996, Hutcheson et al 1998, Haney et al 1999, Kouri et al 1999 and Johns 2001) The prevalence of withdrawal symptoms in chronic cannabis usage was estimated at 16 to 29% (Thomas 1996 and Wiesbeck et al 1996).

More serious withdrawal symptoms, psychiatric problems and aggression, were reported by Teitel 1971, Rohr et al 1989, and Kouri et al 1999.

People using cannabis therapeutically reported uncomfortable feelings on cessation of use (BMA 1997).

Crowley et al in 1997 looked at University-based adolescents in treatment programmes for substance abuse. They involved males and females. 78.6% met the standard criteria for cannabis dependence. Two thirds (over 80% of men and over 60% of women) reported withdrawal symptoms. The progress from first use to regular use was as rapid as tobacco progression and more rapid than alcohol, suggesting cannabis is a reinforcer. All the patients said that cannabis had clearly caused serious trouble in their lives.

Experimental animals had brain changes similar to those resulting from opiate, alcohol and cocaine withdrawal (De Fonseca et al 1997). Laboratory animals (squirrel monkeys) will self-administer doses of THC equivalent to those used by humans. Self-administration by animals has long been considered a model for human drug-seeking behaviour characteristic of virtually all abused and addictive drugs. The drug-seeking behaviour was comparable in intensity to that maintained by cocaine under identical conditions therefore suggesting that marijuana has as much potential for abuse as drugs like heroin and cocaine. (Goldberg et al 2000).

As a result of these findings, cannabis dependence (but not yet "withdrawal conditions following cannabis use" due to continuing disagreement among researchers) was included as a diagnostic unit in the DSM IV (Diagnostic and Statistical Manual of Mental Disorders 1994) and ICD-10, WHO 1992.

The European Description of The ICD-10 Classification of Mental and Behavioural Disorders, WHO, Geneva, 1992 Diagnosis of Cannabinoid Dependence Syndrome, is as follows:

Diagnostic Guidelines

A definite diagnosis of dependence should be made only if three or more of the following have been experienced or exhibited at some time during the previous year.

- *(a) a strong desire or sense of compulsion to take cannabinoid;*
- *(b) difficulties in controlling cannabinoid-taking behaviour in terms of its onset, termination or levels of use;*
- *(c) a physiological withdrawal state when cannabinoid use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for cannabinoid; or use of the same(or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;*
- *(d) evidence of tolerance, such that increased doses of cannabinoid are required in order to achieve effects originally produced by lower doses;*
- *(e) progressive neglect of alternative pleasures or interests because of cannabinoid use, increased amount of time necessary to obtain or take the substance or to recover from its effects;*
- *(f) persisting with cannabinoid use despite clear evidence of overtly harmful consequences, such as depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.*

Narrowing of the personal repertoire of patterns of cannabinoid use has also been described as a characteristic feature.

It is an essential characteristic of the dependence syndrome that either cannabinoid taking or a desire to take cannabinoid should be present, the subjective awareness of compulsion to use drugs is most commonly seen during attempts to stop or control substance use.

Morgenstern et al in 1994 found the DSM concept at least as valid as those for dependence found in opiates, alcohol, stimulants and sedatives.

Jan Ramstrom who wrote "Adverse Health Consequences of cannabis Use", A Survey of Scientific Studies published up to and including the Autumn of 2003 said, "…there is now general agreement on the issue of cannabis and dependence including the importance of withdrawal symptoms".

One recent paper seems to buck the trend of the general acceptance of cannabis addiction and the fact that it is a recognised diagnosable condition. In 2002, NT Smith published a review paper in "Addiction". "This review highlights the methodological weaknesses in some of the literature on this subject ie variable levels of drug dose administration in laboratory conditions, lack of controlled studies and absence of definitions of the withdrawal syndrome. It concludes that more controlled research might uncover a diagnosis of withdrawal symptoms in human users and may be a precedent for the introduction of a cannabis-withdrawal syndrome before the exact root is known".

Coffey et al in 2003 reported that weekly use of cannabis marks the threshold for an increased risk of later cannabis dependency with selection of cannabis in preference to alcohol possibly indicating an early addiction process. She found that 30% of teenagers smoking more than one a week became addicted by their early twenties, those between 14 and 17 were 20 times more likely. Those starting between 14 and 15 progressed to the most harmful use. Almost 66% of teenagers smoke cannabis and about 7% show signs of dependence. The more they smoke, the higher the risk. Interestingly, dependent cannabis users reported compulsive and out-of-control use more frequently than dependent alcohol users, withdrawal to a similar extent and tolerance considerably less often.

Chambers and others in a paper in 2003 on the development of the adolescent brain, warned of their increased vulnerability to addiction compared to adults. He suggested that drug addiction should be thought of as a development disorder in the brains of teenagers, as the changing brain circuitry leaves them especially vulnerable to the effects of drugs and alcohol. This brain circuitry is centred on the chemical (neurotransmitter) dopamine. Parts of the brain changing rapidly during adolescence are stimulated by addictive drugs. The circuitry that releases chemicals that associate novel experiences with motivation to repeat them develops far more quickly in adolescence than the mechanisms that inhibit urges and impulses. Drugs tapping into this neural imbalance may underlie a teenager's affinity for impulsive and risky behaviour. They are more likely to experiment with drugs but the experience will have more profound effects, sometimes permanent, on the brain. "You have a situation where the motivational brain areas are particularly active", he said, "and the part of the brain that is supposed to inhibit impulses is not working well, because it is sort of under construction. The parts of the frontal cortex that are activated by adults when they weigh risks and rewards lag developmentally".

A definitive review of the addictive propensity of cannabis was undertaken in 2003 by Eliot L Gardner. He reviewed 224 scientific papers, 75 of which were published in the 1970s and 80s and the other 149 after 1989. He concluded that "cannabinoids act on the brain reward processes and reward-related behaviours in strikingly similar fashion to other addictive drugs".

And a review of papers (55 references) dealing with withdrawal symptoms was published in 2004 by Budney, Hughes and others. " Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol. …..The onset and time course of these symptoms appear similar to those of other substances withdrawal symptoms. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance".

Continuing their work, Budney and Hughes have just (2006) contributed again to our knowledge of the withdrawal syndrome in cannabis. In their "Purpose of review" they say, "The demand for treatment for cannabis dependence has grown dramatically. The majority of the people who enter treatment have difficulty in achieving and maintaining abstinence from cannabis". Among their findings are, "The neurological basis for cannabis withdrawal has been established via discovery of an endogenous cannabinoid system, identification of cannabinoid receptors, and demonstrations of precipitated withdrawal with cannabinoid receptor antagonists. Laboratory studies have established the reliability, validity and time course of a cannabis withdrawal syndrome and have begun to explore the effect of various medications on such withdrawal. Reports from clinical samples indicate that the syndrome is common among treatment seekers". Another research report by Budney in Addiction 101 (suppl.1) 2006, found that "…cannabis dependence is much more similar to than different from other types of substance dependence, even with regard to withdrawal. The generic DSM-1V dependence criteria can be applied fairly well to cannabis , and yield findings similar to that observed with other substance dependence disorders….whether we can do better by developing more sophisticated generic criteria or using substance specific criteria".

In a paper still in press (2006), Budney et al say, " The demonstration of a dose-dependent suppression of cannabis withdrawal by oral THC provides additional support for validity of the cannabis withdrawal syndrome and its inclusion in the DSM".

Several papers have been written on the extent and prevalence of cannabis dependence.

Young Americans were followed for 13 years from the 7th 8th or 9th grade in school. At 27 to 29 years old just under 24% abused cannabis and just over a quarter of them were addicted, ie 8% of the total population (Newcomb 1992).

A North American population study of 20,000 people reported that, of the 4.4% who abused cannabis roughly 60% were dependent on it. That is about 2.6% of the population (Hall et al 1994) And in a letter to The Lancet in 1998 Hall and Solowij wrote that, of those who ever start using cannabis, 10% will become daily users and 20 to 30% will use it weekly.

In 2003 Fergusson et al, following up 1265 children born in Christchurch, New Zealand for 21 years, concluded that, for the majority of users, cannabis did not lead to problems of dependence. Nonetheless, nearly 10% of the cohort showed clear signs of cannabis dependence by age 21, especially males who were prone to other forms of risk-taking behaviour.

On Sunday June 13th 2004 The Observer carried a story that increasing numbers of people were becoming dependent on the drug. Department of Health figures recorded 9% of attendees at clinics cited cannabis as their problem drug, twice the number ten years before. Research from the United States showed that cannabis is the commonest reason for 12 to 17 year olds to be placed in treatment centres – 60% of all cases. Treatment for cannabis dependence or habitual usage among youngsters had risen 142% in a decade.

Dr Romeo Ashruf, a Dutch addiction specialist and Director of the Parnassia Clinic in The Hague, told Network 2's Bijous Theis TV programme on March 20th 2006 that Dutch children as young as 12 were addicted to cannabis. The powerful home-grown nederwiet they are using is up to 20 times stronger in its THC content than imported varieties. Referrals used to be for young people between 16 and 21, but are now for 14 to 19 year olds. He warned parents of the difference in strength of the drug today.

Cambridge University Press has recently (2006) published a book "Cannabis Dependence: Its Nature, Consequences and Treatment in the series: *International Research Monographs in the Addictions, which*
"Breaks through the controversial politics of cannabis use to give a clear, scientific synthesis of all the Health-related issues relating to cannabis use".
" Reviews and assesses all the interventions applied to both adult and adolescent users".
"Gives the criteria for diagnosis and scope of cannabis dependence".

In 2006 Copersino et al looked at 104 non-treatment seeking adults, primarily cannabis users who had made at least one serious attempt to stop using the drug. "Study findings provide evidence for the clinical significance of a cannabis withdrawal syndrome, based on the high prevalence and co-occurrence of multiple symptoms that follow a consistent time course and that prompt action by the subjects to obtain relief, including serving as negative reinforcement for cannabis use" They said that these findings support the existence of a clinically significant cannabis withdrawal syndrome , which should be considered for inclusion in the DSM-V.

An article in The Ottawa Citizen on 24/11/06 reported that Psychiatrist Kathy Szirtes, speaking at a "Dazed and Confused" forum for teenagers in Rideau High School, said that adults may take 2 years to become addicted to marijuana while children can take only about 6 months as their brains are still not properly developed. Marijuana cravings she said were often mistaken for symptoms of ADHD. The forum was sponsored by the CAMC, Champlain Addiction Coordinating Body and Ottawa Integrated Drugs and Addictions Strategy.

CB1 gene variants may be linked with symptoms of marijuana dependence in adolescents. Hopfer and others found that 2 CB1 variants (present in 12% of the population) were significantly linked to the likelihood of the development of one or more dependent symptoms and another variant (present in 21%of the population) was linked to a lower risk of dependent symptoms developing. DNA samples were taken from 541 youths aged 17 or over who had recently used marijuana at least 5 times. 327 had one or more symptoms of dependence, the other 214 became the controls.

Chronic abuse of different drugs cause similar brain changes. Whether long-term users favour cocaine, cannabis or PCP, autopsies of their brains show a number of common gene changes consistent with diminished brain plasticity (ability to learn from new experiences and adapt to new situations). A paper by Lehrmann and others found that the anterior pre-frontal cortex (decision-making region) was dysfunctional in the brains of drug users. The brains of 42 deceased abusers were studied. Nearly 80% of them had similar alterations in genetic output compared to the controls. Genes involved in calcium signalling were turned down and those in lipid and cholesterol-related pathways were turned up. The abuser's ability to make sound decisions could be threatened.

2006: Nocon et al examined prospectively over 4 years, the profile of cannabis dependence and the risk of specific dependence criteria in a community sample of 2446 young people between 14 and 24. 30% were users of cannbais. 35%met at least one dependence criterion, withdrawal 17%, tolerance 15%, lossof control 14%, and continued use despite a health problem 13%. Even 22% of low frequency users met one criterion, as did 81% of high frequency users. The occurrence of dependence could not be attributed to the concomitant use of other illicit drugs or dependence on alcohol or tobacco.

Over 2500 adult daily cannabis users completed an Internet survey. Fewer than half of daily cannabis users meet the DSM-IV-TR criteria for cannabis dependence. This study aimed to determine whether the negative aspects associated with use of cannabis can be explained by a proxy measure of dependence instead of by frequency of use. Comparing those who were dependent (N=1111) with those who were not

(N=1770), the former consumed greater amounts of cannabis, various other drugs and alcohol. They also exhibited higher levels of depression and lower levels of happiness, motivation and satisfaction with life. The study concluded, " Although all of our subjects reported daily use, only those meeting proxy criteria for cannabis dependence reported significant associated problems. Our data suggests that dependence need not arise from daily use, but consuming larger amounts of cannabis and other drugs undoubtedly increases problems" (Looby and Earleywine 2007).

A paper from STASH (Science Threads of Addiction, Substance Use and Health), January 2007, looked at the transition from drug use to dependence. Over 8000 participants were involved in the study (a report of 3 papers). The probabilities of initiation of drug use peaked at age 18 for alcohol and marijuana. The risk of developing dependence on these drugs also peaked in the teens. Male marijuana users were approximately twice as likely to become dependent in the 2 to 5 years after first use than female users.

A plant extract which may block cannabis addiction has been discovered. MLA (methyllycaconitine) from the seeds of Delphinium brownie, a plant in the buttercup family was given to rats. They lost their craving for a synthetic version of THC and a reward response to THC was blocked in the brain. By analysing fluid from the nucleus acumbens in the reward signalling area of the brain they found that release of dopamine was blocked by MLA. It is not known exactly how MLA works but no side-effects were reported. Dopamine levels were not reduced below the normal. (Goldberg S et al 2007).

A review paper on Marijuana Dependence and its Treatment by Budney and others was published in December 2007. They concluded that the "good news" was the increased recognition that cannabis can cause addiction. Significant negative consequences in a sub-set of users has resulted in specific marijuana-related treatments and interventions similar to those used for other substance disorders. More people are now seeking help as it is now perceived to be acceptable to do so. Rapid advances in the neurobiology associated with marijuana and the cannabinoid system bring hope for increasingly effective treatment options. More severe dependence may be prevented in some users and better contacts made with users who may benefit.

Vandrey et al compared withdrawal symptoms from cannabis and tobacco in a paper in January 2008. They concluded that, "Overall withdrawal severity associated with cannabis alone and tobacco alone was of a similar magnitude. Withdrawal during simultaneous cessation of both substances was more severe than for each substance alone, but these differences were of short duration and substantial individual differences were noted. These results are consistent with other evidence suggesting cannabis withdrawal is clinically important and warrants detailed description in the DSM-V and ICD-11".

2007 Adult Psychiatric and Morbidity Study: The prevalence of drug dependence was 3.4% (4.5%of men, 2.3%of women). Most dependence was on cannabis only (2.5%), rather than other drugs (0.9%). Symptoms of dependence were most commonly reported by adults aged between 16 and 24 (13.3%)of men, 7.0%of women in this age group).

In 2008 (May) Walden and Earleywine found that the quantity of cannabis used predicts future problems with dependence, social factors and respiratory health. Nearly 6,000 adults using at least once a month reported on levels of intoxication and quantity used. Quantity was found to be an important predictor of these 3 problems.

It should be pointed out that most people in Northern Europe smoke cannabis with tobacco. Addiction to nicotine, according to some experts is one of the most difficult to treat and certainly many smokers seem to find it almost impossible to give up. This "double addiction" would significantly exacerbate the problems of giving up cannabis.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) in their annual report in 2010 found that 'Factors specifically associated with progression to dependence include intensive or risky patterns of cannabis use, persistent use and early onset. Individuals who experience positive effects (e.g. laughter, happiness) of their early cannabis use (at age 14-15) had an increased risk of cannabis dependence later in life'.

James Langton smoked cannabis for 30 years. He said, "When I was smoking cannabis it was the most important thing in my life. More important than my family, my friends, my relationships or my job. …. When I was without it, I was irritable, anxious and could concentrate on little else until I was stoned

again….if you had asked me at any time over that long period whether I was addicted to the stuff, I would have laughed in your face and denied it. I knew, as everyone knew at the time, that cannabis wasn't addictive. …"….Apart from denial, fear is the other factor that reinforces cannabis addiction…I was terrified of physical withdrawal. ….disrupted sleep, night sweats, cramps, nausea and loss of appetite. Other symptoms are closer to nicotine withdrawal such as mood swings, irritability and depression".

He has now set up "Clearhead", a new privately funded organisation offering support and information to those seeking to make positive changes in their lives regarding their use of cannabis. He has a website and runs weekend workshops.

2011 Lopez-Larson et al looked at prefrontal and insular cortical thickness in adolescent users. 18 heavy users were compared with 18 non-users. 'Our results suggest that the age of regular use may be associated with altered prefrontal cortical gray matter development in adolescents. Furthermore reduced insular cortical thickness may be a biological marker for increased risk of drug dependence'.

2011 Vanderbilt Addiction Center researchers found that exercise can curb marijuana use and cravings. 12 participants, all cannabis-dependent (av 5.9 joints/day) and not willing to have treatment exercised by running on a treadmill. Their cravings for and use of cannabis were cut by more than 50% after exercising on the treadmill for 10 sessions of 30 minutes each over a fortnight. The maximum reduction occurred in the first week, and overall fell to 2.8 joints/day.

2011 November Levine et al looked at nicotine as a gateway drug. Epidemiological evidence has pointed to the fact that most illicit drug users report use of tobacco or alcohol prior to illicit drug use. The aim was to discover a possible biological mechanism by which nicotine exposure increases the vulnerability of people to illicit drug use. Mice exposed to nicotine in their drinking water for at least 7 days, showed an increased response to cocaine. The nicotine changes the DNA structure, re-programmes the expression pattern of specific genes especially the FosB gene that has been related to addiction and so ultimately alters the behavioural response to cocaine. The 2003 Nat Epidemiological Study of Alcohol-related consequences was examined. The rate of cocaine dependence was higher among cocaine users who smoked prior to cocaine use than those who tried cocaine first before smoking. 'Now that we have a mouse model of the actions of nicotine as a gateway drug, this will allow us to explore the molecular mechanisms by which alcohol and marijuana might act as gateway drugs' said Kandel, 'in particular if f there is a single common mechanism'.

2012 Moghaddam compared the brain activity of adolescent and adult rats involved in an activity in which they expected a reward. Increased activity occurred in an unusual area in the adolescents – the Dorsal Striatum (DS) – a site associated with habit forming, decision-making, motivated learning. Adult rats did not show this. The nucleus accumbens, traditionally associated with reward, was similarly activated in adults and young. Electrodes were implanted into the brains. Reward expectancy is processed differently in adolescent brains but it can affect regions directly responsible for decision-making and action selection. 'Adolescence is a time when the symptoms of most mental illnesses – such as schizophrenia and bipolar and eating disorders – are first manifested, so we believe that this is a critical period for preventing these illnesses'.

2011 Allsop et al looked at the development of a 'Cannabis Withdrawal Scale'. Results showed that the scale had excellent psychometric properties. Nightmares and/or strange dreams was the most valid item but caused relatively little associated distress. Unlike intense angry outbursts which caused much associated distress. Inability to get to sleep caused significant distress. They concluded that 'The Cannabis Withdrawal scale can be used as a diagnostic instrument in clinical and research settings where regular monitoring of withdrawal symptoms is required'.
2013 NIDA researchers suggested that medication to treat marijuana addiction may be on the horizon. Kynurenic acid is a naturally occurring substance in the brain that can lessen the effects of THC in animal models of drug abuse and addiction. If effective in humans, this could lead to a medication for the treatment of marijuana addiction.

2013 Hurd et al provided an overview of the endocannabinoid system in relation to cannabis exposure and provide insightsregarding factors such as genetics and behavioural traits that confer risk for subsequent addiction. Current evidence suggests that the long-term impact of adolescent cannabis exposureon brain and behaviour has a far-reaching influence on adult addictive behaviours particularly for certain subsets of vulnerable individuals.

2014 April NIDA found that marijuana use may promote nicotine consumption.
Most marijuana users smoke cigarettes, and about 1 in 5 individuals who use both substances (1 in 3 among African Americans) used marijuana first. In one recent study, adolescents who used marijuana weekly were more likely than less frequent marijuana users or nonusers to initiate tobacco use. These patterns occur in part because some of the same personal traits and social and environmental exposures that lead people to use marijuana also influence them to try other drugs. The new findings (on rats) suggest that marijuana use itself, independently of these influences, predisposes users to become regular smokers, increasing their odds of becoming addicted to nicotine.

2014 March, Van der Pol and others found that the behaviour of smokers is more important than the potency of their pot (amount of THC) for predicting who will become dependent. Smokers of pot varieties did inhale less smoke and they smoked at a slower pace. They 'titrated' their THC intake but not sufficiently to fully compensate for the THC strength so users of more potent cannabis are generally exposed to more THC. Smoking behaviour appears to be a stronger predictor of cannabis dependence severity than THC content.

2014 September 2nd Greene and Kelly found that cannabis withdrawal symptoms are common in adolescents treated for substance use disorder. A study by Massachusetts general Hospital found that 40% of cannabis-using adolescents receiving outpatient treatment for substance use disordrer experienced withdrawal symptoms. 127 adolescents (14-19) were studied, 90 with cannabis as their most frequently used drug – 84% met the criteria for cannabis dependence. 36(40% of the overall) of them reported withdrawal symptoms, all of whom also met the criteria for dependence.

2015 Freemnan and Winstock looked at high-potency cannabis and its association with severity of cannabis dependence as demand for treatment in addiction services continues to rise. They found that frequent use of high-potency cannabis predicted a greater severity of dependence and this effect became stronger as age decreased. Its profile is strongly defined by negative effects (memory, paranoia), but also positive characteristics – best high, preferred type. It is also the most available.

2016 Gelernter et al looked at genes related to cannabis addiction, depression and schizophrenia. The genes of nearly 15,000 people from 3 different groups. Between 18% and 36% had cannabis addiction. One of the genes was linked to risk for both depression and marijuana addiction. They also found a marijuana-addiction gene related to risk for schizophrenia.

2016 Freeman looked at addiction and super-strength cannabis (skunk). More than 400 adolescents and young adults (aged 16-23) in the UK using marijuana were studied. 43% of the participants who smoked skunk were dependent on the drug while 22% who used less potent types were dependent.

2020 Bahji et al investigated the Prevalence of Cannabis Withdrawal Symptoms Among People With Regular or Dependent Use of Cannabinoids

Abstract: Data Extraction and Synthesis All abstracts, full-text articles, and other sources were reviewed, with data extracted in duplicate. Cannabis withdrawal syndrome prevalence was estimated using a random-effects meta-analysis model, alongside stratification and meta-regression to characterize heterogeneity.
Main Outcomes and Measures Cannabis withdrawal syndrome prevalence was reported as a percentage with 95% CIs.

Results Of 3848 unique abstracts, 86 were selected for full-text review, and 47 studies, representing 23 518 participants, met all inclusion criteria. Of 23 518 participants included in the analysis, 16 839 were white (72%) and 14 387 were men (69%); median (SD) age was 29.9 (9.0) years. The overall pooled prevalence of CWS was 47% (6469 of 23 518) (95% CI, 41%-52%), with significant heterogeneity between estimates ($I^2 = 99.2\%$). When stratified by source, the prevalence of CWS was 17% (95% CI, 13%-21%) in population-based samples, 54% in outpatient samples (95% CI, 48%-59%), and 87% in inpatient samples (95% CI, 79%-94%), which were significantly different ($P < .001$). Concurrent cannabis ($\beta = 0.005$, $P < .001$), tobacco ($\beta = 0.002$, $P = .02$), and other substance use disorders ($\beta = 0.003$, $P = .05$) were associated with a higher CWS prevalence, as was daily cannabis use ($\beta = 0.004$, $P < .001$).
Conclusions and Relevance These findings suggest that cannabis withdrawal syndrome appears to be prevalent among regular users of cannabis. Clinicians should be aware of the prevalence of CWS in order to counsel patients and support individuals who are reducing their use of cannabis.

2020 Leung et al the prevalence and risk of cannabis use disorders among people who use cannabis. We conducted a systematic review of epidemiological cross-sectional and longitudinal studies on the

prevalence and risks of CUDs among cannabis users. We identified studies published between 2009 and 2019 through PubMed, the Global Burden Disease (GBD) Database, and supplementary searches up to 2020. The outcomes of interest were CUDs based on DSM or ICD criteria. Estimates were synthesized using random-effects *meta*-analyses, followed by *meta*-regression of study characteristics on effect sizes. Results From 1383 records identified, 21 studies were included. Meta-analyses showed that among people who used cannabis, 22% (18–26%) have CUD, 13% (8–18%) have CA, and 13% (10–15%) have CD. Estimates from cohort studies, showed that the risk of developing CD increased to 33% (22–44%) among young people who engaged in regular (weekly or daily) use of cannabis. There was a lack of data from cohort studies to estimate the risk of CUD or CA among regular cannabis users. Conclusions Cannabis users need to be informed about the risks of developing CUDs and the higher risks among those who initiate early and use frequently during adolescence. Future studies are needed to examine how changes in cannabis policies may affect the risks of CUDs in the population.

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Cannabis and the Gateway Effect

The question as to whether cannabis "encourages" the use of other drugs has occupied the minds of researchers for the last 30 years or so. It is a very important one since if true, the use of cannabis would be much more dangerous than the effects of the cannabis use alone.

Tobacco and/or alcohol use in teenagers makes the use of other drugs more likely (Merrill et al, 1994) and the same is true of cannabis. A MORI poll in 1991 found that 50% of smokers had tried an illegal drug compared to only 2% of non-smokers and Califano (2003) concluded that young cigarette smokers were 14 times more likely to try pot. Cigarette smoking was discovered to be an important predictor of both the initiation and persistence of cannabis use. A report published in December 2006 by the Canadian Centre on Substance Abuse "Risks Associated with Tobacco Use in Youth Aged 15-19", an analysis of the data from the Canadian Addiction Survey, 2004, found that 91% of smoking youth reported using cannabis in the past year compared with 28.8% of non-smoking youth. And compared with 3.5% of non-smoking youth, 31% of smokers below 20 (including the 15 to 19 year olds) reported using cocaine, amphetamines, heroin, ecstasy or hallucinogens in the past year.

Professor Denise Kandel and her team in America have researched this subject for many years. Early in her work she found a series of graded steps that most of her subjects followed. There were four:
1.Beer and wine 2.Cigarettes and spirits 3. Marijuana 4. Other illegal drugs (Kandel, 1989).
The younger they started, the further they progressed and the more intense the abuse at any age the greater the risk of progression to the next stage. Of those who had used cannabis more than 1000 times, 90% moved on to other drugs. Between 100 and 1000 it was 79%, dropping to 51% between 10 and 100 times. Even 1 to 9 times usage saw 16% follow this path. Of non-users, only 6% eventually used drugs other than cannabis. (Kandel, 1986).

Among other researchers to discover a link between use of cannabis and use of other drugs are: Aas and Pederson, 1993, Von Sydow, et al 2001 and Brook, et al 1989 (The East Harlem Study of African-American and Puerto Rican 14 year old adolescents). In a large longitudinal study, 36% of a group of 27 to 29 year-olds were found to be dependent on both marijuana and cocaine (Newcomb, 1992). Kleber (1995) said that 60% of young Americans using marijuana before the age of 15 will use cocaine later in life, and those between 12 and 17 who use cannabis are 85 times more likely to use cocaine than non-smokers of the same age.

"The statistical association between the intensity of cannabis consumption and the likelihood of using hard drugs strengthens the case for assuming that there is a causal connection between cannabis smoking and progression to harder drugs, but it does not constitute proof of such a causal link…….. The general impression, then, has been that the imperative role of cannabis in the "stepping stone" model has resisted all attempts to prove it scientifically. On the other hand, a large body of circumstantial evidence has been gathered. It is found time and again that cannabis is a central component of the network of influencing factors that leads to the abuse of hard drugs" (Ramstrom, 2003).

To sum up, support for the gateway effect is as follows: 1. Marijuana users are many times more likely than non-users to progress to hard drug use. 2. Almost all who have used marijuana and hard drugs have used marijuana first (Yamaguchi and Kandel, 1984) 3. The greater the frequency of marijuana use, the greater the likelihood of using marijuana later.

Explanations for the gateway effect include the following:

1. Changes in brain chemistry that may make young people more susceptible.
2. Experiences with cannabis may encourage experimentation with other drugs.
3. Common factors in personality or background.
4. Cannabis use is illegal so supplies come from the illegal market, bringing exposure of young people to drug dealers.

Dr Patrick Dixon in his book The Truth About Drugs (1998), says, "Common sense tells us there is a link…….We know that once teenagers start smoking tobacco it is easier for them to cross the next step and smoke cannabis". My pupils used to tell me, "Find a smoker and you will find a cannabis user". The smoking technique has been learned. Dr Dixon also said, "……once someone starts using cannabis it is easier for them to try something else, and for the following reasons:

Desensitisation: “It was a big step at first, but cannabis didn’t kill me – actually I can’t see what all the fuss is about so why not try some other things?”

Targeting by dealer: “My mate offered me some free dope and also had some other stuff he was giving away so I tried both”

Knowledge of supply: “I was thinking about trying something else and I already knew who to ask”.

Drug-taking part of social life: “My friends do things together. We all smoke dope. Someone had something else so for a bit of a laugh we all tried it”

“It is dangerous nonsense therefore to suggest that cannabis use does not significantly increase the risk of a serious drug addiction later on” (Dixon, 1998).

Exactly the same sentiments were expressed to me by an ex-pupil, an ex-user. “Cannabis didn’t seem to have much effect and didn’t harm us so we looked for a bigger and better high. We tried more or less everything that was going except heroin”. (Crack cocaine was not around at the time).

The “personality and background predisposition hypothesis” was explored by Degenhardt and others in 2001. They looked at 201 15 to 16 year olds who had used cannabis at least 40 times. They found 3 “clusters” of heavy users. There was a small group with anti-social behaviour, another with low self-esteem and poor relationships with their parents and friends, the third group were “ordinary”. This last group were the least likely to use other illicit drugs.
Information from 44624 individuals of between 12 and 25 was gathered. These people did not seek out drugs but were “exposed” to the opportunity of taking them at a party or friend’s home. Users of tobacco and alcohol were more likely than non-users to have the opportunity to try marijuana and indeed were more likely to take it. Opportunities to try cocaine were associated with prior marijuana smoking. Among the young people who had a “cocaine opportunity”, those who had used marijuana were more likely to use cocaine than those with no previous history of using cannabis. They also found that by the age of 21, half the teenagers who had smoked marijuana had a chance to try a hallucinogenic drug, LSD, mescaline, PCP or mixed-stimulant-hallucinogens, compared to only 1 in 16 of non-users. Within one year of “exposure” two-thirds of the cannabis-users had tried it, but only 1 in 6 of those who had never smoked cannabis (Wagner and Anthony, 2002).

Two separate twin studies explored the “family environment/genetic influence”.

In 2003, Lynskey and others examined 311same-sex twins (identical and non-identical) in Australia. They were discordant for cannabis use before the age of 17. The twin using cannabis before 17 had odds of other drug use, alcohol dependence and drug use/dependence that were 2.1 to 5.2 times higher than their co-twin who was a non-user of cannabis prior to the age of 17. No significant differences were found between mono- and di-zygotic twins. Controlling for early alcohol or tobacco use, parental conflict/separation, childhood sex abuse, conduct disorder, major depression and social anxiety had negligible effects of the outcome. So common environmental and genetic influences seemed not to be predisposition factors. Association with different peers and the social contexts in which cannabis was used may have some bearing on the results.

2004 Agrawal et al looked at twins. They concluded: Early cannabis use is strongly associated with other illicit drug use and abuse/dependence. The relationship arises largely due to correlated genetic and environmental influences with persisting evidence for some causal influences.

In 2006 Lynskey, again with a team, conducted research into twins this time of Dutch nationality, 219 same-sex pairs, discordant for cannabis use before 18 were used. Covariants were adjusted. The rates of lifetime party drug use, use of hard drugs, but not regular cannabis use, were significantly higher in the pre-18 using twin. Again this suggested that the progression seen is not explained by common familial risk factors, genetic or environmental. Different friends or social experiences obviously could play a part.

Professor David Fergusson and his teams have conducted a long-term longitudinal study in New Zealand, The Christchurch Health and Development Study. It has followed 1265 children from birth in the middle of 1977. They have been regularly assessed till the age of 21 with an 80% follow-up (Fergusson et al, 1997, 2000, 2002).

At the age of 18, the associations for the "gateway question" did not appear to be very strong when all other factors were taken into account. However at 21, more data were available and methods of analysis were more advanced. For young 14 to 15 year old heavy consumers a very strong association existed even after controlling for other suspected or known causal factors. It was the first time such a strong connection had been seen (Fergusson et al, 2002). By the age of 21 nearly 70% of the cohort had used cannabis and 26% other drugs. In all but 3 cases, cannabis use came first. Those using cannabis on 750 occasions/year had hazards of other illicit drug use 59.2 times higher than non-users. After adjustments for co-variants, childhood, family and adolescent lifestyle factors, the association was still remarkably strong. Fergusson points out that, "…findings support the view that cannabis may act as a gateway drug that encourages other forms of illicit drug use. Nonetheless the possibility remains that the association is non-causal and reflects factors that were not adequately controlled in the analysis".

In April 2006 Ferguson updated his results. The sequence of events he said could suggest a cause and effect relationship where the use of cannabis encourages the use of other illicit drugs. He points out that it has often been suggested that associations between cannabis and other illicit drug use arise from common factors that predispose young people to using cannabis and other drugs. However, he says, this study applied complex statistical methods and controls and still found a clear tendency for those using cannabis to have higher rates of usage of other illegal drugs. It was most evident for regular users and more marked in adolescents than young adults.

Looking for a neurophysiological explanation rather than a psychosocial mechanism, the phenomenon of sensitisation, an "inverse tolerance effect" was suggested as long ago as 1999 by Torngren. This is the process by which an addictive substance increases a person's sensitivity to the exhilarating effects of that substance. This process exists in humans and has been shown in animals. Exposure to one substance e.g. cannabis, should be able to make a person more sensitive to another substance like heroin (cross-sensitisation). At the moment, he said, this remains hypothetical reasoning.

Professor Heather Ashton, Emeritus Professor of Clinical Psychopharmacology at The University of Newcastle-on-Tyne, puts forward mechanisms for the association which may favour a causal role for cannabis. They are:
1. Tolerance to the "high" leading users to seek more potent drugs.
2. Withdrawal symptoms being alleviated by the use of other drugs.
3. Interaction of cannabinoids with the endogenous opioid systems which have been shown in animals to increase the rewarding properties of opioids such as heroin.

(Ashton 2002)

Professor Robin Murray of The Institute of Psychiatry in London commented (The Daily Telegraph 18/06/05), " Clearly it needs to be replicated but there is already evidence that, in animals, cannabis and amphetamine show cross-tolerance. So that rodents given THC, the active ingredient of cannabis, show greater effects when given amphetamine".

A 2006 paper by Maldonado, Valverde and Berrendero has shown that the endocannabinoid system (neurotransmitters mimicked by THC) is involved in the common neurobiological mechanism underlying drug addiction in three ways.

1. The system participates in the primary rewarding effects of nicotine, alcohol, opioids and cannabinoids through the release of endocannabinoids in one part of the brain (the ventral tegmental area).
2. Endocannabinoids are also involved with motivation to seek drugs through a dopamine-independent mechanism (this has been demonstrated for psychostimulants and opioids).
3. The common mechanisms responsible for relapse into drug-taking behaviour also include the participation of endocannabinoids. This is done by mediation of the motivational effects of drug-related stimuli in the environment and exposure to drugs.

Professor Yasmin Hurd (2006) warns that the human brain is not fully developed till around the age of 25. Chronic periodic use of cannabis can interfere with the development of rat brains. She says, "The developing brain is definitely more sensitive". After training rats to self-administer heroin by pushing a lever, rats exposed to THC took more heroin than those not previously exposed to it. They were more sensitive to lower concentrations of heroin and took more in response to stress. Her conclusion reads: The current findings support the gateway hypothesis demonstrating that adolescence cannabis exposure has an enduring impact on hedonic processing resulting in enhanced opiate intake, possibly as a consequence of alterations in limbic opioid neuronal populations".

The December 2006 edition of Alcoholism: Clinical and Experimental Research carried an article about smoking among adolescents and an increased risk of developing alcohol-use disorders. Results indicate that smoking "primes" the brain for subsequent addiction to alcohol and possibly other drugs. Almost 75,000 adolescents and young adults were randomly selected for the study by Grucza and Chen. Typically teenage smokers had a 50% higher risk of developing an alcohol-use disorder (a range of problems including alcohol abuse and alcohol dependency). Grucza said, " Addictive drugs all act on a part of the brain that is described as the central reward circuitry. Once this system is exposed to one drug, the brain may become more sensitive to the effects of other drugs, as demonstrated by a number of rodent studies. Our results are in line with an emerging literature that shows adolescence may be a unique window of vulnerability for addiction".

In February 2007 a Swedish paper by Ellgren set out "to determine whether cannabis exposure during periods of active brain development alters reward-related behaviour and neurobiology for psycho-stimulant and opioid drugs by the use of animal models". Results did not support the cannabis gateway hypothesis in relation to subsequent psycho-stimulant use but did support it in relation to opioids. The typical pattern of intermittent use by adolescents was mimicked and discrete opioid-related alterations were revealed in brain regions highly implicated in reward and hedonic processing. This was coupled to increased heroin intake in a self-administration paradigm, and increased morphine conditioned place preference, indicating altered sensitivity to the reinforcing properties of opioids. In the limbic region, there were pronounced alterations in endocannabinoid levels in cognitive brain areas even though alterations were also apparent in reward-related regions. Pre-natal exposure induced discrete opioid-related alterations within brain regions highly implicated in reward and hedonic processing.

They concluded, "Taken together, this thesis presents neurobiological support for the cannabis gateway hypothesis in terms of adult opiate, but not amphetamine abuse, with underlying long-term disturbances of discrete opioid-related systems within limbic brain regions".

In the light of all the evidence, it is obvious that every effort must be made to try to prevent vulnerable children from ever starting to use cannabis, not least because of the potential damage done by cannabis itself.

October 23 2007 brought a report from The National Center on Addiction and Substance Abuse at Columbia University. (CASA), "Tobacco: The Smoking Gun". They found that "Compared to 12 to 17 year olds that don't smoke, those who do are more than 5 times likelier to drink and 13 times likelier to use tobacco than non-smokers. Those who begin smoking at age 12 or younger: More than three times liklier to binge drink; nearly 15 times liklier to smoke marijuana and nearly 7 times liklier to use other illegal drugs such as heroin and cocaine". The nicotine poses asignificant danger of chemical and structural changes in the developing brain. This can make a teenager more susceptible to alcohol and other drug addiction and mental illness.

A paper by Patton et al in 2007 found in a 10-year 8-wave cohort study of 1943 Victorian children, originally 14 to 15, that heavy (daily) teenage cannabis users tend to continue selectively with cannabis use. "Considering their poor young adult outcomes, regular adolescent users appear to be on a problematic trajectory."

In 2008 (April) Fergusson et al updated their findings from The Christchurch Longitudinal Study. Their results showed that "Illicit drug use and abuse/dependence from ages 16 to 25 were significantly associated with a range of parental adjustment measures; exposure to abuse in childhood; individual factors; and measures of childhood and early adolescent adjustment. Analyses…suggested that parental illicit drug use, gender, novelty-seeking and childhood conduct disorder predicted later illicit drug use and abuse/dependence. Further analysis revealed that these pathways to illicit drug use and abuse/dependence were mediated via cannabis use, affiliation with substance-using peers, and alcohol use during ages 16-25". In their conclusion they said, "the use of cannabis in late adolescence and early adulthood emerged as the strongest risk factor for later involvement in other illicit drug use".

2010 June 2010 Melberg et al (Norwegian researchers) tested the "gateway" hypothesis. 'The model they chose suggests two distinct groups; a smaller group of "troubled" youths for whom there is a statistically significant gateway effect that more than doubles the hazard of starting to use hard drugs, and a larger faction of youths for whom previous cannabis use has less impact'.

2010 A study from Australia by Degenhardt et al found that occasional cannabis use in adolescence predicts later drug use and eductional problems. Nearly 2000 secondary school pupils were followed from 14.9 to 24 years of age. Those who continued cannabis use into early adulthood had higher risks of later adult alcohol and tobacco dependency and illicit drug use, as well as being less likely to complete a post secondary qualification.

2011 (July) Swift et al found that quitting cannabis in your twenties cuts progression to other drugs. Use of cannabis declines among Australians throughout their twenties but Those who are still using are more likely to be weekly users or even more frequent. They have an increased risk compared with occasional users. Weekly users – risk of other illicit drugs – 2 to 3 times, daily – 6 times as likely to smoke tobacco and less likely to give up all others except cocaine. Nearly 2000 Victorian secondary school pupils followed for 13 years, from 1992. Six, six monthly intervals, then 20-21, 24-25, and 29. While overall decrease (age 20 – 58% to only 29% at 29) in cannabis use in young adults, number of those who use weekly/daily almost doubled. Among non-users, use of ampthetamines, cocaine or ecstasy virtually non'existent.

2012 Mayet looked at the influence of cannabis use patterns on the probability of subsequent initiation with other illicit substances among French adolescents. 29,393 teenagers were studied. All possible pathways were modelled from initial abstinence to cannabis initiation, daily cannabis use and OID 9other illicit drugs) initiation. The model was adjusted for tobacco and alcohol use. The risk for OID initiation was 21 times more with experimenters, 124 times higher among daily users than non-users. Tobacco and alcohol were associated with a greater risk of moving on to cannabis.

2012 September. Agrawal looked at 3797 sets of twins in Australia and siblings between 21 and 46 to find out whether cigarette smokers were at increased likelihood of early opportunity to use cannabis and early onset of cannabis use. They found that regular users were more likely to report an earlier opportunity to use cannabis and early onset of cannabis use. Conclusion: These findings indicate that the well-known overlap in cannabis and cigarette smoking behaviours may evolve as early opportunity to use and extend through the course of the substance use trajectory.

2013 Fiellin found that 'previous alcohol, cigarette and marijuana use were each associated with current abuse of prescription opiods in 18-25 year old men, but only marijuana use was associated with subsequent use of prescription opioids in young women'.

2013 Palamar . Data was obtained from over 29,000 high school seniors who took part in the 'Monitoring The Future' Survey. He found that youths who smoked cigarettes or used more than one hard drug were consistently less critical of other drug use. The lifetime use of alcohol had no impact on peoples' attitudes. Those who used only marijuana were less judgemental of further using of such so-called socially acceptable drugs such as LSD, amphetamines and ecstasy. They did not approve of crack, cocaine or heroin. Females and religious people had much less approval of drug use. Youths from more advantaged socio-economic backgrounds with highly educated parents and those who live in urban areas were much less disapproving of the so-called 'less-dangerous' drugs.
Black students are less disapproving of powdered cocaine, crack and ecstasy. They use this type of drug less than white people. This could be influenced by their strong religion and higher rates of arrest and incarceration than whites which may act as a deterrent.

2014 Tzilos et al investigated co-occurring drug use among marijuana users. 1075 'emerging adults' were studied. Daily marijuana use was associated with a significant increase in the expected odds of opiate, cocaine, stimulant, hallucinogen, inhalant and tobacco use. They may be vulnerable to additional negative consequences associated with poly-substance use.

2014 Secades-Villa et al looked at the 'gateway' effect of cannabis. 6624 participants who had used cannabis before any other drug (Wave 1 of The National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Lifetime cumulative probability estimates that 44.7% of individuals with lifetime cannabis use progressed to other illicit drugs at some time in their lives. There was an increased risk of progression amongst those with mental illness disorders.

2015 Szutorisz et al found that rats, whose parents had been exposed as adolescents to the main psychoactive ingredient in marijuana (THC) sought heroin more vigorously than the offspring of unexposed animals. This suggests that a parent's history of drug abuse, even preconception, may affect a

child's brain function and behaviour. It was thought that these alterations in the THC-exposed rats' offspring may be due to epigenetic factors.

2015 May, Badiani et al looked at tobacco and cannabis use for evidence of reciprocal causal relationships, using date from the Christchurch Health and Development Study (CHDS). Significant associations between the extent of cannabis use and tobacco smoking and vice versa, after controlling for non-observed fixed confounding factors and for a number of time-dynamic covariate factors (major depression, alcohol use disorder, anxiety disorder, stressful life events, deviant peer affiliations) were found. Furthermore, increasing levels of tobacco smoking were associated with increasing cannabis use and vice versa over time. The results lend support to the notion of both of 'gateway' and 'reverse gateway' effects. That is, the association between tobacco and cannabis use arises from a reciprocal feedback loop involving simultaneous causation between tobacco use disorder and cannabis use disorder.

2016 Weinberger et al found that marijuana users were 5 times more likely to develop an alcohol use disorder, alcohol abuse or dependency. The researchers analyzed data from 27,461 adults enrolled in the National Epidemiologic Survey on Alcohol and Related Conditions who first used marijuana at a time when they had no lifetime history of alcohol use disorders. The population was assessed at two time points. Adults who had used marijuana at the first assessment and again over the following three years (23 percent) were five times more likely to develop an alcohol use problem, compared with those who had not used marijuana (5 percent). Adult problem drinkers who did not use cannabis were significantly more likely to be in recovery from alcohol use disorders three years later.

2016 Blanco et al looked at cannabis use and the risk of psychiatric disorders. Respondents in the US aged 18 or over, mean age 45.1 years, were interviewed 3 years apart. Cannabis use in 'wave 1' (2001-2) reported by 1279 respondents, was significantly associated with substance use disorders in 'wave 2' (2004-5). Any substance use disorder OR (Odds Ratio) 6.2, any alcohol use disorder OR 2.7, any cannabis use disorder OR 9.5, any other drug use disorder OR 2.6 and nicotine dependence OR 1.7. No mood disorder OR1.1 or anxiety disorder OR 0.9. Cannabis use is associated with an increase for several substance use disorders.

2016 Osborne analysed information from more than 11,000 children (10-18) from 10 American cities. They were asked whether they had used prescription opioids in the last 30 days and whether they had ever used cannabis. About 29% said they had used cannabis at some point in their lives, but among the 524 participants who had used prescription opioids in the last 30 days, nearly 80% had used cannabis. Among those who had used non-prescription opioids, about 88% had used cannabis compared to 61% who had had it prescribed. Teens reporting opioid use as well as alcohol and tobacco were much more likely to have used cannabis. The opioid users using alcohol were nearly 10 times more likely to have used cannabis, and those who currently smoked tobacco were 24 times more likely to have used cannabis. More males were at risk than females.

2017 Ninneman et al Investigated whether depression, alcohol and marijuana use was linked to use of synthetic cannabinoids (SC) among teens. 964 high-school students participated and completed questionnaires a year apart. The researchers found that depressive symptoms but not anxiety or impulsivity were predictive of later SC. The same relationship between depressive and greater propensity for marijuana use was not found.

2017 Otten et al looked at the gateway theory and friendship associations. 'This longitudinal study analyzed 3 waves of data from a community sample of 711 male and female participants without a history of illicit drug use reporting drug use at age 17, 22, and 27. Substance use assessments including tobacco, alcohol, cannabis, onset and abuse/dependence tendency of illicit drugs other than cannabis (i.e., cocaine, methamphetamine, and opiates), and friends' reported use of illicit drugs. Participants' cannabis use level at age 17 was positively associated with perceived friends' drug use at age 22, which in turn predicted participants' onset of illicit drug use between ages 22 and 27. Moreover, progression of tobacco use throughout age 17 to 22 was associated with an increased onset of illicit drug use between ages 22 and 27. Apart for an effect of cannabis use at age 22 on abuse and dependence tendency to various drugs at age 28, results were similar.During this period of development, the availability and selection of drug-using friends contributes to the progression to potentially more rewarding and damaging illicit drugs'.

2017 Taylor et al looked at any possible l;inks between teen cannabis use and illicit drug use in early adulthood. They used data from The Avon Longitudinal Study of parents and Children (ALSPAC). 5315 teens between 13 and 18 were examined over 5 years at one year apart. Cannabis use was classified as none, occasional (typically less than once/week) or frequent (once/week or more). At the age of 21 they

(1571 with complete data) were asked questions about their habits. 462 reported recent illicit drug use, 176 (38%) had used cocaine, 278 (560%) had used amphetamines, 136 (30%) inhalants72% sedatives 105 (23%) hallucinogens and 25 (6%) opioids. After taking account of confounding factors, regular users were 37% more likely to be nicotine dependent, and 3 times more likely to have a harmful drinking pattern than non-users by 21 and were 26 times more likely to use illicit drugs. They concluded one in five adolescents follow a pattern of regular or occasional use and they are more likely to be tobacco dependent, have harmful levels of alcohol consumption or use other illicit drugs in early adulthood.

2020 Williams investigated cannabis as a gateway drug for opioid use disorder. Cannabis use in some individuals can meaningfully introduce *de novo* risk for the initiation of opioid use and development of opioid use disorder. These risks may be particularly high during adolescence when cannabis use may disrupt critical periods of neurodevelopment. Current research studying the combination of genetic and environmental factors involved in substance use disorders is poorly understood. More research is needed, particularly to identify which adolescents are most at risk and to develop effective interventions addressing contributing factors such as trauma and psychiatric co-morbidity.

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Effects of Cannabis Use on the Reproductive system, Pregnancy and Development of Children

In the mid-seventies animal experiments suggested that cannabis adversely affects the secretion of gonadal hormones in both males and females, and the foetal development of animals given THC during pregnancy (Bloch 1983, Nahas 1984, Nahas and Frick 1987, Wenger et al 1992).

Research was triggered by the reporting of gynecomastia (breast development) in 3 young men (23 to 26) all heavy cannabis users (Harmon 1972). These findings are now in doubt as a small case-controlled study failed to find a relationship in 11 cases and controls (Cates and Pope 1977), and Mendelson (1984) said there would surely be more cases as the number of young men using cannabis was high.

Kolodny and others investigated men who were chronic cannabis users in 1972. They had reduced plasma concentrations of testosterone, sperm count and motility, with an increased number of abnormal sperm. Bloch 1983, Wenger 1992, and The National Academy of Science 1982, gave support to all his findings with experiments on animals.
Wenger said they were either due to the action of THC on the testes and/or the brain hormones that stimulate sperm production.

Kolodny's results were contradicted by Mendelson and others in 1974 in a large well-controlled study of heavy users. Other studies have produced positive and negative findings of the effect of THC on testosterone.

Although the reductions in testosterone and sperm numbers observed in some studies may not be of great significance in healthy adults, Hollister (1986) argued that they could pose problems in pre-pubertal males. A boy of 16, smoking cannabis since the age of 11, suffered from retarded development of the secondary sexual characteristics and growth. Partial recovery was attained 3 months after stopping (Copeland et al 1980). Also men with already impaired fertility may be at risk.

Dr Lani Burkman of Buffalo University Medical School, New York, reported to the annual meeting of The American Society of Reproductive Medicine in San Antonio, Texas on October 13th 2003. She had looked at the sperm of 22 frequent cannabis users (14 times a week for at least 5 years) and compared it with that of 59 men, non-users who had children. She found that the sperm were moving too fast, too soon. They would "burn out" before they reached the egg and would be unable to fertilise it. She suggested this may be a cause of infertility. She also found the users produced fewer sperm.

Studies on female fertility have also produced conflicting results. Bloch found that on exposing non-pregnant animals to THC, there was interference with the hormones concerned in reproduction produced in the brain. Oestrus was delayed, as was ovulation by a reduction of luteinising hormone and an increase in prolactin secretion. Rozenkrantz (1985) said exposure of pregnant women to THC was too risky as it may damage the foetus. Conflicting results have also been obtained on the cycling of sex hormones and duration of menstrual cycles in women.

The blastocyst stage of the embryo has to be implanted in the uterus wall for its continued development. Anandamide, the neurotransmitter mimicked by THC is produced at a high level in the uterus before implantation and then down-regulated at the time of implantation. High levels of anandamide induce spontaneous pregnancy loss in women. The use of cannabis at this crucial time during pregnancy may have the same effect (Paria et al 2001, Wang et al 2003).

A paper in 2006 (Klonoff-Cohen et al) on the effects of marijuana use on the outcomes of IVF (In Vitro Fertilisation) and GIFT (Gamete Intra-Fallopian Transfer) fertility treatments found that the prospect of a good outcome is reduced if either of the partners uses marijuana. Females produced fewer eggs and the child had a significantly lower birth weight, the more recent the use, the worse the effects. Male marijuana use was also associated with lower birth weight. Both timing and amount of the drug used negatively affected IVF and GIFT.

The risk of miscarriage or ectopic pregnancy of women smoking cannabis in the early stages of pregnancy was highlighted in recent research by Dey and others in 2006. Anandamide controls the development of the embryo so the level of the neurotransmitter is crucial. THC by mimicking anandamide disrupts the correct signaling process. The embryos of mice treated with THC had more cell abnormalities than the controls and

the embryos failed to travel to the uterus.

THC passes through the placenta in animals and humans, so it could potentially damage the embryo (Bloch 1983, Blackard and Tennes 1984). It is also passed in breast milk (Astley and Little 1990).

Experiments on animals have shown a number of very serious effects on gestation of offspring born to females given THC during pregnancy. These results must lead to a consideration of the possibility of similar effects occurring in humans (Abel 1985). In another paper in 1985 Abel found that a combination of alcohol and marijuana caused 73% fetomortality (offspring deaths) in rats and 100% in mice.

There is now consistent evidence to show that habitual cannabis smoking during pregnancy is associated with a lower than average birth weight (Hatch and Bracken 1986, Zuckerman et al 1989, Sherwood et al 1999) and height (Zuckerman et al 1989 and Tennes 1985) the relationship persists after control for confounding variables. Gibson and his colleagues in 1983 looked at the cases of 36 women, using cannabis 2 or more times/week. Twenty five per cent of them had premature births. An increased risk of prematurity was also found by Sherwood et al 1999.

Earlier experiments before the mid-eighties, not surprisingly produced inconsistent results as they were often conducted with insufficient care.

In 1995 Shiono and others failed to find any significant association between marijuana smoking and birth weight, however when the mothers blood was tested a clear tendency towards lower birth weight was apparent.

An analysis of 10 different studies into the effects of cigarette smoking in 1997, 7 of which involved cannabis use, displayed only a weak association between cannabis use and birth weight. For any use of the drug the average reduction was 48g. Use 4 times a day averaged 131g loss of weight. They concluded that the difference was small compared to the effects on birth weight of tobacco smoking, and that there is inadequate evidence that cannabis at the amount typically consumed by pregnant women, causes low birth weight (English et al 1997).

There are enormous problems in conducting surveys of this type. Heavy use of cannabis during pregnancy is rare, many samples are too small (Greenland et al 1982a/b, Fried 1980). Because of its illegality, many women are unwilling to be honest about their drug taking so lots of them will be classed as non-drug users (Zuckerman et al 1989). They are also likely to use alcohol, tobacco and other illegal drugs and tend to belong to a different social class (Fried, 1980, 1982, Tennes 1985). But the greatest problem is small numbers.

In 2002 the Avon Longitudinal Study of Parents and Children team in Bristol (Fergusson et al) looked at 12000 mothers expecting single babies. On average the babies were 216g lighter for women smoking once a week, they were significantly shorter and had smaller heads. When other factors were taken into consideration the average reduction in weight dropped to 90g. They equated the effect of a weekly joint to that of 15 cigarettes.

In animals very high doses of marijuana were needed to increase the rate of malformations occurring in the offspring. And indeed some experiments found this association (Linn et al 1983). Bloch (1983) found that in sufficient dosage, re-absorption, growth retardation and other malformations occurred in rats, rabbits mice and hampsters. But most of the best-designed studies failed to confirm these findings. Zuckerman et al in1989 discovered among 202 infants, pre-natally exposed to marijuana, a rate of malformations no higher than in a control group of non-using mothers. Gibson et al 1983, Hingson et al 1982 and Tennes et al 1985, uncovered no increase in the rate of major congenital abnormalities in children born to marijuana-using mothers.

Abel (1985) and Bloch (1983) suggested the malformations may be due to reduced nutrition due to the very high doses of the drug. Hollister (1986) added that “Virtually every drug that has ever been studied for dysmorphogenic effects has been found to produce these if the dose is high enough, enough species are tested or the treatment is prolonged”.

However many of the papers that exonerate cannabis use were conducted using marijuana and not THC at the start of the eighties when the THC content of the marijuana widely used was very low. And Hall and others warned in 1994 that, “It would be unwise to exclude cannabis as a cause of malformation until larger

and better-controlled studies have been carried out".

Malformations could of course be caused by chromosome damage. It has not been possible to show that THC can produce effects on specific genes which can cause abnormalities (Hall 1994, Hollister 1986). Cannabis smoke on the other hand is mutagenic (Bloch 1983). Hollister (1986) and The Institute of Medicine (1982) both discounted evidence that cannabinoids may cause mutations.

Three studies in the late eighties and early nineties linked cannabis use to an 11-fold increase in the cases of one form of leukaemia, ANNL (Acute Nonlymphoblastic Leukaemia) born to mothers using cannabis during pregnancy and increases in two other forms of childhood cancer, rhabdosarcoma and astrocytomas (Robison et al, 1989 Neglia al 1991, Grufferman et al 1993). The children with ANNL were younger than children with the disease born to non-using mothers and had cell differences which the researchers said made it unlikely that the relationship was due to chance.

There is little literature on the subject of the development of children whose mothers had smoked cannabis while pregnant. One study, unique in its longevity, The Ottawa Prenatal Prospective Study has been carried out from 1978 to the present day by Dr Peter Fried and his team. The children were examined neurologically immediately after birth and again several times in their first year. Tests for cognitive and psychomotor functioning were then executed yearly. At first, signs of neurological development deficiencies were detected, a delay in the development of the visual system and an increased rate of tremors and startle, as were withdrawal symptoms. These disappeared and nothing was reported till the age of four when memory and verbal ability were found to be deficient. At 5 and 6 these seemed to have gone but the six year olds had impaired ability to sustain attention.
From 6 to 9, several deficits in cognitive functions were noted and the parents reported behavioural problems. Between 9 and 12, there was a reduced ability as "regards memory in connection with visual stimuli, analytical ability and integrative ability". Again attention maintenance was a problem. The same pattern emerged from 13 to 16 (Fried 2003).

Fried et al in 1992 found that marijuana use increases the symptoms of ADHD in first grade children. Six year old children are more likely to show signs of this condition if their mothers smoked 6 or more marijuana cigatettes /week.

Fried said that the damage inflicted by cannabis at the foetal stage would not be noticed until the child needed to use his or her "executive" functions (for problem-solving and planning) at the age of four. Leavitt et al (1994) and Lundqvist (1995) found similar deficits in adult cannabis users. Fried also warns that the marijuana in 1978 when his investigation began had a much lower average THC content, so the risks may now be higher. On 15th July 2006 Dr Fried is due to give a talk at The 13th World Conference on Tobacco OR Health in Washington DC. As part of his long running study, he will say that children of mothers who smoked marijuana while pregnant are more than twice as likely to take up the habit when they reach adolescence.

Dahl (1995) had found sleeping problems in 3 year olds and Day (1994) lower intelligence scores also at the age of 3. These findings support those of Fried.

Another long-term study has been published. Goldschmidt and others in 2002 gathered data from over 250 women who used cannabis while pregnant. Reports from parents and teachers were used and at age 6 the teachers reported problems with delinquent behaviour. At 10, questionnaires were distributed and interviews conducted. A clear relationship between exposure to cannabis and delinquency was established, manifested by attention deficits, impulsiveness and hyperactivity.

Tennes and others in 1985 studied over 200 women who had used cannabis during pregnancy. The children were monitored after birth and again at one year old. They failed to find any differences between them and the controls.

An Italian research team under Vincenzo Cuomo (2003) injected pregnant rats with a low dose of artificial cannabinoid. The offspring were hyperactive. This disappeared at adulthood but was replaced by learning and memory retention problems. Because rats do not have confounding factors like tobacco smoking, standard of living or alcohol use, the results can be very useful. Fried said this showed great consistency with his study on humans.

The most recent study on the effects of pre-natal marijuana exposure (Day et al September 2006) has

concluded that, " Prenatal exposure to marijuana , in addition to other factors, is a significant predictor of marijuana use at age 14". Other variables controlled for were: the child's current alcohol and tobacco abuse, pubertal stage, sexual activity, peer drug use, delinquency, family history of drug abuse and parental depression, current drug use, strictness and levels of supervision.

In 2002, Nahas and others reported that THC damages the formation of DNA in the dividing cells of testes and has been shown to impair the development of sperm cells in man. Marijuana or THC produces an early apoptosis of these fast-dividing cells and THC-induced apoptosis has also been found to occur in cells of the immune system (Zhu et al, 1998). Apoptosis is the "programmed cell death" of all our cells as they grow older, it is an irreversible biological process.

THC accumulates in fatty tissues and there are huge reserves of fat in the body for THC storage. With regular marijuana smoking the THC will build up quickly and take about 30 days to be completely eliminated. There will thus be a constant slow release of THC that will affect any processes going on in the body. Nahas concluded, " During chronic exposure to THC the pharmacokinetic molecular mechanisms which limit the storage of THC in the brain and testes are not sufficient to prevent a persistent deregulation of membrane signalling and the induction of functional and morphological changes which reflect a premature apoptosis of spermatogenic cells. Long-term longitudinal epidemiological studies have reported decreased spermatogenesis in healthy fertile adults".

Referring to 25-year old research findings on cannabis and the reproductive process detailed in his book Marijuana and Medicine 1999, Nahas said, "The latest studies in molecular biology have demonstrated that THC, the active ingredient in marijuana, damages the earliest stages of reproductive function. Thus marijuana is gametotoxic (toxic to embryos and sperm). It kills the reproductive cells of seven animal species, produces damage to the embryo, and retards foetal development. All of these destructive effects of marijuana on sperm cells, embryonic cells or lymphocytes have now been related to the early production of "apoptosis", the programmed death of the cell".

Frequent maternal marijuana use may be a weak risk factor for Sudden Infant Death Syndrome, SIDS (Scragg et al 2001).

In 2002 in The Princess Royal Maternity Hospital in Glasgow, drug tests (from the first stools) were carried out on 400 newly born babies. One in eight was found to have been exposed to cannabis in the womb. The study was carried out by forensic scientists from Glasgow University (Dr Ghada Abd-El-Azzim and Dr Robert Anderson), paediatric consultants (Lesley Jackson and Charles Skeoch) and senior registrar Scott Williamson. About 130 babies every year are treated at the hospital for drug dependency. Treatment can take days, weeks or months. According to the Forensic Science International Journal, more than 75% of babies exposed in this way will have medical problems later in childhood compared to 27% of the unexposed infants (Sunday Post 15/12/02).

A paper by Schuel et al in 2002 found evidence that anandamide signaling regulates human sperm functions required for fertilization. An analogue of AEA (anandamide) and also THC modulated capacitation and fertilizing potential of human sperm in vitro, sperm fertilizing capacity (in the Hemizonsa assay) was reduced by 50%. " These findings suggest that AEA-signaling may regulate sperm functions required for fertilization in human reproductive tracts, and imply that smoking of marijuana could impact these processes.

2002 Richardson and others looked at prenatal exposure to alcohol and marijuana and the effects on 10 year-old neuropsychological outcomes. At 10 over 500 children from a longitudinal study were tested for problem solving, learning, memory, mental flexibility, psychomotor speed, attention and impulsivity. Prenatal marijuana use had an effect on learning and memory as well as impulsivity.

2003 Williams et al looked at maternal lifestyle factors and risk for ventricular septal defects. Abstract: 'The Atlanta Birth Defects Case–Control Study was used to identify 122 isolated simple VSD cases and 3029 control infants born during the period 1968 through 1980 in the metropolitan Atlanta area. Exposure data on alcohol, cigarette, and illicit drug use were obtained through standardized interviews with mothers and fathers. Associations between lifestyle factors and VSD were calculated using maternal self-reports; associations were also calculated using paternal proxy-reports of the mother's exposures. RESULTS: Maternal self-report of heavy alcohol consumption and paternal proxy-report of the mothers' moderate alcohol consumption were associated with isolated simple VSD. A two-fold increase in risk of isolated simple VSD was identified for maternal self- and paternal proxy-reported cannabis use. Risk of isolated

simple VSD increased with regular (three or more days per week) cannabis use for both maternal self- and paternal proxy-report, although the association was significant only for maternal self-report. CONCLUSIONS: This is the first study to identify an association between maternal marijuana use and VSD in offspring. Further studies are needed to elucidate this'.

2005 Gray et al looked at prenatal exposure and effects on depressive symptoms at age 10. 633 mother/child dyads were studied. Exposure to marijuana in the first and third trimesters predicted significantly increased levels of depressive symptoms (rather than a diagnosis of a major depressive disorder).

A review article was written in 2006 (Huizink and Mulder). They came to the conclusion; that pre-natal exposure to either maternal smoking, alcohol or cannabis use is related to some common neurobehavioural and cognitive outcomes, including symptoms of ADHD (inattention, impulsivity), increased externalising behaviour, decreased general cognitive functioning, and deficits in learning and memory tasks.

Bluhm et al in 2006 found that maternal recreational use of drugs and marijuana during pregnancy were associated with increased risk of neuroblastoma in offspring.

Barros and colleagues, writing in The Journal of Paediatrics in January 2007 found that marijuana-exposed infants born to adolescent mothers scored differently on measures of arousal, regulation and excitability compared to non-exposed infants, they showed subtle behavior changes in the first few days of life, they cried more, startled more easily and were more jittery. The authors said this may interfere with mother-child bonding.

Harkany et al in a paper in January 2007 found that endocannabinoid signaling modulates CNS (Central Nervous System) patterning so that "pharmacological interference with endocannabinoid signals during foetal development leads to long-lasting modifications of synaptic structure and functioning. Marijuana abuse during pregnancy can impair social behaviours, cognition and motor functions in the offspring with the impact lasting into adulthood.

Another paper in May 2007 had similar findings. Endocannabinoids in the human body play a vital role in the development of a baby's brain. They are responsible for controlling how the complex system of nerves develop in the embryonic brain. Dr Ann Rajnicek said "Smoking cannabis could interfere with the signals that are being used in the brain to wire it up correctly in the first place. As the brain develops further, there will be functional problems – potential brain damage" (Berghuis P et al 2007).

Forrester and Merz found selected birth defects with prenatal drug use in a study in Hawaii. December 2007. Cases were infants/fetuses with any one of 54 selected birth defects delivered during 1986-2002. Marijuana rates were significantly higher than expected for 21(39%) of the birth defects. These defects were associated with the CNS, cardiovascular system, oral clefts, limbs and the gastrointestinal system.

A paper in March 2008 by Goldschmidt et al found that intelligence test performance was adversely affected at the age of 6 in children born to cannabis-using mothers. 648 children were involved in the study. Women were questioned about their use of marijuana at 4 and 7 months of pregnancy and at delivery. The results were: 'There was a significant nonlinear relationship between marijuana exposure and childhood intelligence. Heavy marijuana use (one or more cigarettes per day) during the first trimewter was associated with lower verbal reasoning scores on the Stanford-Binet Intellegence scale. Heavy use during the second trimester predicted deficits in the composite, short-term memory and quantitative scores. Third trimester heavy use was negatively associated with the quantitative score. Other significant predictors of intelligence include maternal IQ, home environment and social support'. They concluded that, "These findings indicate that prenatal marijuana exposure has a significant effect on school-age intellectual development".

2008 Aversa looked at erectile dysfunction in young habitual cannabis users. When cannabis is smoked, the arteries are constricted by a small amount. In long-term abusers, the arteries become so constricted that blood cannot properly flow to the penis. Men who chronically abuse marijuana show links to impotence since there is damage to the penile endothelium vasodilation and dilatation of brachial arteries. Dr. Aversa and his research team have concluded that, "early endothelial damage may be induced by chronic cannabis use (and endocannabinoid system activation)."

2008 April, Ian Russell, a specialist nurse practitioner in andrology and urology at Dumfries and Galloway Royal Infirmary in Scotland said, " In my clinic I see youngsters from the age of 17 onwards with sexual

dysfunction. The age of onset of smoking cannabis is young, 10 years old in some areas. Puberty's kicking in and they're smoking regularly – 5,6 joints a week. This can potentially suppress and traumatize the formation of leydig cells which secrete testosterone in the testes. This means these kids when they hit 14 or 15, will have sexual problems, for instance, not being able to get an erection, and possibly not having any sexual desire and a very very low testosterone level.

2008 Viagra is being prescribed for young men who use cannabis. The NHS in Scotland now spends £25m on Viagra, in some areas there is a 20% rise. There has been a rise in the number of teenage boys seeking help for erectile dysfunction. Two experts have now linked this increase with cannabis use. Ian Russell, an expert on sexual health at Dumfries and Galloway Royal Infirmary, revealed more Scottish teens than ever before are suffering impotence after smoking cannabis during puberty, and Derek Rutherford, a specialist in sexual medicine for NHS Ayrshire and Arran, said he had prescribed Viagra to cannabis smokers.

2009 van Gelder et al looked at maternal preconceptional illicit drug use and the risk of congenital malformations. Abstract: We analyzed data from the National Birth Defects Prevention Study, a case-control study of major birth defects, and assessed all birth defects categories in which there were at least 250 interviewed case mothers. We included 10,241 infants with major congenital malformations (case infants) and 4,967 infants without major congenital malformations (control infants) born between 1997 and 2003 for whom there was a completed maternal interview with detailed information on prenatal illicit drug use and potential confounders. We used multivariable logistic regression to estimate the associations between cannabis, cocaine, and stimulant use in the month before pregnancy or during the first trimester (periconceptional period) and the occurrence of selected birth defects. In the periconceptional period, 5% of the 15,208 mothers reported any use of illicit drugs. We did not find associations between illicit drug use and most of the 20 eligible categories of congenital malformations. Periconceptional cannabis use seemed to be associated with an increased risk of anencephaly (adjusted odds ratio _ 1.7; 95% confidence interval _ 0.9 –3.4), whereas cocaine use in the periconceptional period was associated with the risk of cleft palate (2.5; 1.1–5.4). There were very few suggestions of positive associations between periconceptional illicit drug use and the 20 birth defects categories

I recently was in conversation with a midwife who had delivered babies of cannabis-using mothers. She said, "They are ravenous, chew their hands constantly, drink 3 times as much milk as non-affected babies, are promptly sick, then hungry again.

January 2010 El Marroun et al again found that maternal cannabis use even for a short period in pregnancy may be associated with lower birthweight and head circumference, and this this was more pronounced than the growth restriction seen in tobacco users. 7.5 thousand women were assessed.

2010 Gray et al: 86 pregnant women provided details of daily cannabis and tobacco use during pregnancy. Cannabis exposure was associated with decreased birth weight, reduced length and smaller head circumference, even after control for tobacco c-exposure.

2010 Campolongo et al looked at the developmental consequences of perinatal cannabis exposure - neuroendocrine and behavioural effects in adult rodents.
Conclusions: 'There is increasing evidence from animal studies showing that cannabinoid drugs are neuroteratogens which induce enduring neurobehavioral abnormalities in the exposed offspring. Several preclinical findings reviewed in this paper are in line with clinical studies reporting hyperactivity, cognitive impairments and altered emotionality in humans exposed in utero to cannabis. Conversely, genetic, environmental and social factors could also influence the neurobiological effects of early cannabis exposure in humans'.

2010 Willford et al looked at prenatal tobacco, alcohol and marijuana, and their effects on processing speed, visual-motor coordination, and interhemispheric transfer. 320, 16-year olds, taking part in a longitudinal study into effects of prenatal substance exposure on development outcomes were investigated. No interactions were found between the 3 substances. Confounding factors were controlled for. There were significant and independent effects of the 3 on processing speed, and interhemispheric transfer of info. Tobacco and marijuana were implicated with deficits in visual-motor coordination.

2011 Shamloul reviewed the medical literature on cannabis use and sexual health. He revealed that cannabis use may negatively impact male sexual performance. While it was previously known that cannabis could affect certain receptors in the brain , it's now believed that these receptors also exist in the penis. Cannabis use may have an antagonizing effect on these receptors in the penis, making it more difficult for a man to achieve and maintain an erection.

2011 Day and others looked at the effects of prenatal marijuana exposure (PME) on delinquent behaviour. 580 mother/child dyads were used from the 4th prenatal month through 14 years. Offspring of heavier marijuana users were significantly more likely to report delinquent behaviour at age 14. The odds ratio for delinquency for those exposed to one or more joints per day during gestation was 1.76. PME significantly predicted child depressive symptoms and attention problems at 10, after controlling for other significant covariants. Child depressive symptoms and attention problems at 10 significantly predicted delinquency at 14 years. The association between PME and delinquent behaviour at 14 years was mediated by depressive symptoms and attention problems in the offspring at 10 years.

2011 Frank et al studied the impact of intrauterine exposure to substances on initiation of use by adolescents. 149 adolescents who had been exposed to cocaine in the uterus were followed from birth till the age of 16. Higher levels of IUCE (intrauterine cocaine exposure) were associated with a greater likelihood of initiation of any substance (licit or illicit) as well as marijuana and alcohol specifically. Those with lighter intrauterine marijuana exposure had a greater likelihood of initiation of any substance as well as of marijuana particularly. Time dependent higher levels of exposure to violence between ages 8 and 16 were also robustly associated with initiation of any illicit or licit use and of marijuana and alcohol particularly.

2011 April: Marroun and others found, using stats from over 4000 children that intrauterine exposure to cannabis is associated with behavioural problems in early childhood with an increased risk for aggressive behaviour and attention problems as early as 18 months in girls, but not boys. No association was found between cannabis use of the father and child behavoiur problems.

2011 Keimpema and others looked at the pre-natal development of the neuronal system. Endo-cannabinoid signalling orchestrates neuronal differentiation programs through timed interaction with the cannabinoid receptors. Cannabis, through prolonged switching on of these receptors high-jacks the system and leads to the erroneous wiring of neural networks. Cannabis-induced cannabinoid receptor activity over-rides physiological neuro-developmental endo-cannabinoid signals affecting the timely formation of synapses.

2012 Jan, Goldschmidt and others found, in a longitudinal study from birth, that a significant negative relation was found between prenatal exposure to marijuana (PME) and 14 year old WIAT(Wechsler Individual Achievement Test) composite and reading scores. The deficit in school achievement was mediated by the effects of PME on intelligence test performance at 6, attention problems and depression symptoms at 10, and early initiation of marijuana use.

Psychoyos et al in 2012 August found that new high-potency marijuana can interfere with early brain development in developing foetuses. 'Some new high-potency strains, including some medicinal cannabis blends , contain up to 20 times more THC than did 'traditional marijuana from decades past' said Delphine.Psychoyos, the co-author. 'Easy access to drugs via the internet or dispensaries makes the problem worse'. Harmful effects can begin as early as 2 weeks from conception. Exposure to today's marijuana in early pregnancy is associated with anencephaly, a devastating birth defect in which infants are born with large parts of the brain or skull missing.. Early pre-natal use was also tied up with ADHD. learning disabilities, memory problems in toddlers and 10 year olds as well as depression, aggression and anxiety in the teens.

Lacson and others in September 2012 found that marijuana use may increase the risk of developing subtypes of testicular cancer that tend to carry a worse prognosis. This result should be considered not only in people using cannabis recreationally but also when marijuana and its derivatives are used for therapeutic reasons in young male patients. 163 young men diagnosed with testicular cancer were compared with 292 healthy men of the same age and race/ethnicity. The marijuana-using men were twice as likely to have subtypes called non-seminoma and mixed germ cell tumours. These

cancers usually occur in younger men and carry a worse prognosis than the seminoma type. These results confirm those of 2 previous studies of marijuana and testicle cancer.

2013 Fiellin found that 'previous alcohol, cigarette and marijuana use were each associated with current abuse of prescription opiods in 18-25 year old men, but only marijuana use was associated with subsequent use of prescription opioids in young women'.

NHS Statistics Agency December 2013 showed that more than 20 babies/week are born addicted to drugs, including methadone in England. More than 10,000newborns had to put into 'cold turkey' at birth. The number with 'neonatal withdrawal symptoms' has risen by 11% in the past 4 years to 1,129 last year.

2013 Varner et al found that smoking pot may double the risk for stillbirth. Cannabis, smoking, illicit drug use and second-hand smoke exposure are linked to an increased risk for stillbirth. 663 stillbirths were enrolled into the study and 1,900 live births. Cannabis increased the odds of stillbirth by more than twice as much - a 2.8-fold increase.

2013 Capogrosso et al investigated erectile dysfunction. They found that 1 in 4 men seeking help for newly developing erectile dysfunction (ED) was under 40, nearly half of them having a serious condition. ED is common among older men, the prevalence increases with age. Severe ED was found in 48.8% of younger patients and 40% of the older men. Compared with the older men, younger men had a lower average body mass index, a higher average level of testosterone in the blood and a lower rate of other medical conditions (9.6% cf 41.7%). They had also smoked cigarettes and used illicit drugs. Capogrosso P, Colicchia M, Ventimiglia E, Castagna G, Clementi MC, more frequently than older patients.

2014 Szutorisz et al Found that parental THC exposure leads to compulsive heroin seeking etc in the subsequent generation. ' Electrophysiologically, plasticity was altered at excitatory synapses of the striatal circuitry that is known to mediate compulsive and goal-directed behaviour. These findings demonstate that parental history of germ-Szutorisz H, DiNieriline THC exposure affects the molecular characteristics of the striatum, can impact offspring phenotype, and could possibly confer enhanced risk for psychiatric disorders in the subsequent generation'.

2014 Jan Jaques et al in a review of the literature, weeded out the myths of the pregnant woman and her child. Current evidence indicates that cannabis use both during pregnancy and lactation may adversely affect neurodevelopment, especially during periods of critical brain growth both in the developing foetal brain and durinf adolescent maturation , with impacts on neuropsychiatric, behavioural and executive functioning. Future adult productivity and lifetime outcomes may be influenced.

2014 June Pacey et al found that sperm shape and size in young men can be affected by cannabis use. Men who produced ejaculates with less than 4% normal sperm (the current criterium for normal) were nearly twice as likely to have produced a sample in the summer months (June to August) or if they were below 30 or to have used cannabis in the 3 months prior to ejaculation. Alcohol and tobacco had little effect. (Men exposed to paint stripper and lead have similar problems).

2014 Day et al looked at PME (Prenatal Marijuana Exposure), age of marijuana initiation, and the development of psychotic symptoms in young adults. 763 pregnant women who completed the birth assessment in their fourth prenatal month, were selected for follow-up. Women and their offspring were followed till the offspring were 22 years of age (596 offspring were evaluated). PME and EAOM (Early Age Onset Marijuana) significantly predicted increased rates of PS (Psychotic Symptoms) at 22 years of age, controlling for other significant co-variants. They concluded that PME in addition to EAOM, may also play a role in the association between marijuana use and the development of PS.

2014 Warner et al investigated maternal-fetal health and the developing child. This is a summary of their findings:

Evidence about the effects of marijuana use during pregnancy- and fetal-related complications and child development is inconclusive. Data from preclinical studies is suggestive of negative outcomes based on disruptive effects on the endocannabinoid system. The results from longitudinal, prospective studies that started in the late1970s and early 1980s

indicate subtle effects on attention, executive functions, and behavior, particularly as marijuana-exposed youth develop into adolescence and early adulthood. Given that today's marijuana is 6 to 7 times more potent and more likely to
be consumed in greater average amounts by younger users, continued surveillance is warranted and may reveal more significant short-term and long-term harms. The practice of medicine for physicians who care for marijuana-using pregnant women is being shaped by shifting societal pressures. Increasingly, marijuana is being thought of as "medicine" by the general public as evidenced by "medical" marijuana laws. Promarijuana advocacy efforts may lead to perceptions about marijuana as being relatively "safe" and result in increased use by several groups, including pregnant women. At the same time, pregnant women who use illicit drugs and controlled substances such as prescription opioid analgesics are being criminalized and charged with child abuse and other felonies, despite efforts from scientists and medical professionals.Nationwide educational efforts are imperative to ensure women are not misled into believing that marijuana use in pregnancy is without possible danger to the developing fetus. Further research is critical to ascertain the specific risks to the developing fetus both in utero and beyond.

2015Giacomo and others studied the CB2 receptors and spermatogenesis. They found that both hype-r and hypo-stimulation of the CB2 receptors disrupted the temporal dynamics of the spermatogenic cycle. 'These findings highlight the importance of proper CB2 signalling for the maintenance of a correct temporal progression of spermatogenesis and suggest a possible adverse effect of cannabis in deregulating this process.

2015 Warshak et al looked at the association between marijuana use and adverse obstetrical and neonatal outcomes. 6468 women, 6107 non-users and 361 marijuana users were included. They found that maternal marijuana use does not increase the risk of adverse obstetrical outcomes or fetal abnormalities, but does increase the risk for small for gestational age and neonatal intensive care unit admission.

2015 Roth et al looked at marijuana use by pregnant women. Approximately 4.4% of more than 67,000 pregnant women in the USA used illicit drugs while pregnant, marijuana being the most common. Marijuana can enter the bloodstream in seconds, the brain within minutes and cross the placenta to reach the fetus. Repeated marijuana use can alter receptors in the brain during fetal development as early as 2 weeks after conception, leading to problems with attention, memory and problem-solving. It can also affect an infant's birth weight, decrease length of gestation and increase risk for preterm labour.

2016 Carter et al looked at the effects of alcohol, methamphetamine and marijuana exposure on the placenta. All three were associated with distinct patterns of pathology. Marijuana was associated with larger placental weight.

2016 Gunn et al found that cannabis use in pregnancy was linked to low birth-weight and intensive care. Seven research data bases were researched up to 2014. 'Infants exposed to cannabis in the womb were 77% more likely to be underweight at birth and twice as likely to require intensive care'.

2016 Giacomo et al investigated fertility treatment for men. A cannabinoid receptor CB2 helps regulate the creation of sperm. Not only does this provide more evidence that marijuana can disrupt fertility in males, but it also suggests a therapeutic strategy for treating male infertility. Infertility is a worldwide problem that affect up to 15% of couples. Three groups of mice with different agents for 14 to 21 days. The first group was treated with a specific activator of the CB2 receptor. The second group was treated with a specific inhibitor of the CB2 receptor. The third group received only a saline solution and served as the control group. The group treated with the CB2 activator showed an acceleration of spermatogenesis, while the group treated with the inhibitor displayed a slower rate of the process. This suggests that a tight balance of CB2 activation is required for the proper progression of spermatogenesis. That the normal beneficial effects of endogenous cannabinoids on spermatogenesis can be stimulated further by a chemical mimic, an agonist, is a potentially promising new idea for treating male infertility.

2016 Leemaqz et al studied maternal marijuana use and the risk for spontaneous pre-term birth. Women who continue to use marijuana at 20 weeks gestation are 5 times more likely to deliver pre-term than those who do not. Pregnancy outcomes for 5588 women in their first on-going pregnancy were studied, and interviewed at about 15 and 20 weeks of pregnancy. 236 women had spontaneous pre-term births, which is associated with the baby dying after birth or suffering long-term and costly health consequences. 4.5% of the participants used marijuana in the 3 months before pregnancy or during the first half of pregnancy.

2016 Rosevear reported urological problems in his practice in Colorado. Two men after having vasectomies reported experiencing a seizure. They had both used cannabis. A young couple in their twenties reported infertility after a year. The male's sperm showed abnormal morphology, decreased counts and low motility. Again they both confessed to using cannabis, almost daily. A few months later, after abstaining, she conceived.

2016 Chabarria et al explored marijuana and pregnancy. Out of 12,069 pregnant women, 106 reported using marijuana or marijuana plus tobacco. The combination of tobacco and marijuana had a significant effect on increased risk of multiple adverse perinatal outcomes, maternal asthma, pre-term birth, decreased head circumference, and decreased birth weight. Co-users also had elevated risks of pre-eclampsia.

2016 Goldschmidt et al looked at early marijuana initiation, the link between prenatal marijuana exposure, early childhood behaviour, and negative adult roles. PME (Prenatal Marijuana Exposure), child behaviour at 3, early onset of marijuana use (EAOM <15) and adult roles at 22 were investigated. Early childhood behaviour was significantly related to EAOM . EAOM was significantly associated with negative adult roles, including being arrested, lower educational attainment, having a child outside marriage and unemployment at 22. Correlations between PME and negative adult roles and between early childhood behaviour and negative adult roles were also statistically significant.

2016 El Marroun et al looked at cannabis use in pregnancy and brain development in offspring. Children exposed to cannabis before birth had a thicker prefrontal cortex, a region involved in complex cognition, decision-making and working memory. The brains of 54 children, 6-8 years old, pre-natally exposed to cannabis were studied. Since they may also have been exposed to tobacco, 96 children exposed only to tobacco and 113 controls were used. Cannabis has different effects on the cortical thickness than tobacco.

2016 Health Canada warns of specific risks associated with the use of marijuana products for medicinal purposes. Under the age of 25 the product should not be used if allergic to cannabinoid or to smoke, have serious kidney, liver heart or lung disease, personal or family history of serious mental disorders – schizophrenia, psychosis, depression, bipolar disorder, are pregnant, planning to get pregnant or breast-feeding. ARE A MAN WISHING TO START A FAMILY, have a history of alcohol or drug abuse or substance dependence. Marijuana products can blood levels of testosterone, affecting sperm production, enough to render a person sterile. Even if a mother has never used cannabis, DNA damage from cannabis use can be passed on by father's sperm causing serious and fatal illnesses in offspring and may affect future generations. Marijuana may significantly increase a man's risk of developing an aggressive type of testicular cancer. Tends to strike between 20-25 and accounts for 40% of all testicular cancer cases.

2016 Friedrich et al looked at the effects of cannabis on embryological development. Use of marijuana in early pregnancy is associated with many of the same risks as tobacco. – miscarriage, birth defects, developmental delays, learning disabilities, but many more issues need addressing. THC alters molecular pathways that should not be disrupted during foetal development. The fact that THC seems to stop cancer growth by killing cancer cells suggests how damaging it could be to the foetus. The following findings were cited:
THC remains in the body for weeks, readily crosses the human placenta, THC levels have increased nearly 25-fold, THC interferes with the use of folic acid – deficiencies can lower birth weight, increase abortion rates, and cause neural tube defects e.g. spina bifida. Proper signaling for development and implantation of embryo is disrupted, and has been linked with autism and low IQ.

2016 Nielsen et al looked at abuse of alcohol and other illicit drugs and schizophrenia risk. Danish records of 3.1 million people's medical records were investigated. The y found the increased risk of schizophrenia from cannabis (skunk) use was 5.2 times, alcohol 3.4, hallucinogenic drugs 1.9, sedatives 1.7, amphetamines 1.24. and other substances 2.8 times**. In a second study (Hjorthoj et al),** they found that pregnant cannabis-using women had children 6 times more likely to be schizophrenic. For paternal cannabis use there was a 5.5 times increase risk of schizophrenia in the child before/after birth.

2016 Volkow et al looked at the risks of Marijuana Use During Pregnancy. Some cannabis extracts, THC and CBD have been passed for medical use. For example THC(dronabidol and nabilone) have been found to be effective in treating nausea. Increasing numbers of pregnant women are using medical marijuana to combat the nausea of pregnancy, particularly in the first trimester. Infants of women who used marijuana during pregnancy were more likely to be anemic, have lower birth weight and require neonatal intensive care than infants of non-users. Marijuana interferes with neurodevelopment, fetal brain growth and structural and functional neurodevelopment could be affected. The concentration of THC in marijuana has risen greatly in recent years. Physicians and other health care providers should warn about the risks of using marijuana during pregnancy.

2017Mark et al looked at pregnant women and their cannabis use. Results: ‘Of 306 surveys returned, 35% of women reported currently using cannabis at the time of diagnosis of pregnancy and 34% of those women continued to use. Seventy percent of respondents endorsed the belief that cannabis could be harmful to a pregnancy. Fifty-nine percent of respondents believed that cannabis should be legalized in some form and 10% reported that they would use cannabis more during pregnancy if it were legalized. Those who continued to use cannabis during pregnancy were less likely than those who quit to believe that cannabis use could be harmful during pregnancy (26% vs 75%). The most common motivation for quitting cannabis use in pregnancy was to avoid being a bad example (74%); in comparison, only 27% of respondents listed a doctor's recommendation as a motivation to quit’.

2017 Foeller et al looked at marijuana use in pregnancy. Abstract: Marijuana is the most commonly used illicit drug in pregnancy, and the prevalence of use during pregnancy is increasing in the United States. Although much of the existing research investigating marijuana use in pregnancy is limited by study design and confounding factors, a growing accumulation of data suggests adverse outcomes. Studies have identified associations with decreased birth weight, increased spontaneous preterm birth, and impaired neurodevelopment among children and adults with in utero exposure. Moderate concentrations of marijuana have also been identified in breast milk. Due to these findings, multiple professional societies have issued clear statements against marijuana use during pregnancy and lactation’.

2017 Callaghan et al investigated cannabis use and testicular cancer. ‘The study included a population-based sample (*n* = 49,343) of young men ages 18-21 years who underwent conscription assessment for Swedish military service in 1969-1970. The conscription process included a nonanonymous questionnaire eliciting information about drug use. Conscription information was linked to Swedish health and administrative registry data. Testicular cancers diagnosed between 1970 and 2011 were identified by International Classification of Diseases-7/8/9/10 testicular cancer codes in the Swedish National Patient Register, the Cancer Register, or the Cause of Death Register. No evidence was found of a significant relation between lifetime "ever" cannabis use and the subsequent development of testicular cancer [*n* = 45,250; 119 testicular cancers]. "Heavy" cannabis use (defined as usage of more than 50 times in lifetime, as measured at conscription) was associated with the incidence of testicular cancer (*n* = 45,250; 119 testicular cancer cases; The current study provides additional evidence to the limited prior literature suggesting cannabis use may contribute to the development of testicular cancer.

2017 Grant et al investigated the use of marijuana and other substances among pregnant and parenting women with substance use disorders and the changes in Washington State after marijuana legalization**. ‘**In 2012, possession of marijuana for nonmedical use was legalized in Washington State. This study examined how legalization affected alcohol and drug use in a sample of pregnant and parenting women with substance use disorders. Study participants from nine counties in Washington State (N = 1,359) were questioned about their substance use after completing a 3-year case management intervention program. The sample was divided into two cohorts based on whether participants had completed the program before or after legalization. Most study participants reported complete abstinence from alcohol and nonprescription drugs at program exit. Among those who were still using substances, women who completed the intervention after marijuana legalization were significantly more likely to report marijuana use at program exit compared with women who completed the intervention before marijuana legalization. Across both cohorts (pre- and post-legalization), we found a positive association of exit marijuana use with alcohol, illegal methadone, other opioids, amphetamines, and cocaine use; even when we controlled for historical period, the association with some of these substances with marijuana use remained evident. Independent of marijuana use, we saw increased use during the post-legalization period of alcohol, illicit methadone, and other opioids. Marijuana use at exit from the Parent-Child Assistance Program (PCAP) increased significantly after marijuana legalization in the state. Women who were not abstinent from marijuana at program exit were likely to report use of other substances as well. Our study design demonstrates an association but does not allow us to conclude that marijuana use leads to other substance use among this sample of women with a history of polysubstance use.

2018 Crume et al looked at prenatal cannabis use and the association with low birth weights. Data from a survey of 3207 women who participated in the Colorado Pregnancy Risk Assessment Monitoring System in 2014-5. In Colorado the prevalence of marijuana use during pregnancy was 5.7% and 5% among those who were breast-feeding. They also discovered that prenatal marijuana use was associated with a 50% increased chance of low birth weight, regardless of tobacco use. Prenatal cannabis use was 3-4 times higher among those who were younger, less educated, in receipt of Medicaid or WIC, white, unmarried and poor. Between 2002 and 2014, cannabis use in pregnancy has increased 62% while potency has increased 6 or 7-fold since the 1970s. 88% of the women using cannabis were breast-feeding.

2018 Baker et al looked at the transfer of inhaled cannabis into human breast milk. OBJECTIVE: To evaluate the transfer of delta-9-tetrahydrocannabinol and its metabolites into human breast milk after maternal inhalation of 0.1 g cannabis containing 23.18% delta-9-tetrahydrocannabinol. A total of eight women were enrolled. Most were occasional cannabis smokers and one a chronic user. Delta-9-tetrahydrocannabinol was detected at low concentrations at all the time points beyond time zero. No metabolites were detected at any time point. Delta-9-tetrahydrocannabinol was transferred into mother's milk such that exclusively breastfeeding infants ingested an estimated mean of 2.5% of the maternal dose (the calculated relative infant dose=2.5%, range 0.4–8.7%). The estimated daily infant dose was 8 micrograms per kilogram per day. This study documents inhaled delta-9-tetrahydrocannabinol transfer into the mother's breast milk. Low concentrations of delta-9-tetrahydrocannabinol were detected. The long-term neurobehavioral effect of exposure to delta-9-tetrahydrocannabinol on the developing brain is unclear. Mothers should be cautious using cannabis during pregnancy and breastfeeding.

2018 Dickson et al Looked at recommendations from cannabis dispensaries about first-trimester cannabis use. Abstract: This was a statewide cross-sectional study in which advice about cannabis product use was requested using a mystery caller approach. The caller stated she was 8 weeks pregnant and experiencing morning sickness. Dispensaries were randomly selected from the Colorado Department of Revenue Enforcement Division website. The primary outcome was the proportion of marijuana dispensaries that recommended a cannabis product for use during pregnancy. We hypothesized that 50% of dispensaries would recommend use. A sample size of 400 was targeted to yield a two-sided 95% CI width of 10%. Secondary outcomes included the proportion endorsing cannabis use as safe during pregnancy, specific product recommendations, and encouraging discussion with a health care provider. Recommendations were compared by licensure type (medical, retail, or both) Of the 400 dispensaries contacted, 37% were licensed for medical sale (n=148), 28% for retail (n=111), and 35% for both (n=141). The majority, 69% (277/400), recommended treatment of morning sickness with cannabis products (95% CI 64–74%). Frequency of recommendations differed by license type (medical 83.1%, retail 60.4%, both 61.7%, *P*<.001). Recommendations for use were similar for dispensary location (urban 71% vs nonurban 63%, *P*=.18). The majority (65%) based their recommendation for use in pregnancy on personal opinion and 36% stated cannabis use is safe in pregnancy. Ultimately, 81.5% of dispensaries recommended discussion with a health care provider; however, only 31.8% made this recommendation without prompting. Nearly 70% of Colorado cannabis dispensaries contacted recommended cannabis products to treat nausea in the first trimester. Few dispensaries encouraged discussion with a health care provider without prompting.

2018 Schuetze et al looked at prenatal cannabis use and infant size and behaviour. ‘Nearly 30 percent of women who smoke cigarettes during pregnancy also report using marijuana," says Rina Das Eiden, PhD, RIA senior research scientist. "That number is likely to increase with many states moving toward marijuana legalization, so it's imperative we know what effects prenatal marijuana use may have on infants." Eiden studied nearly 250 infants and their mothers. Of these, 173 of the infants had been exposed to tobacco and/or marijuana during their mothers' pregnancies. None were exposed to significant amounts of alcohol. Eiden found that infants who had been exposed to both tobacco and marijuana, especially into the third trimester, were smaller in length, weight and head size, and were more likely to be born earlier, compared to babies who were not exposed to anything. They also were more likely to be smaller in length and weight compared to babies exposed only to tobacco in the third trimester. The results were stronger for boys compared to girls."We also found that lower birth weight and size predicted a baby's behavior in later infancy," Eiden says. "Babies who were smaller were reported by their mothers to be more irritable, more easily frustrated and had greater difficulty calming themselves when frustrated. Thus, there was an indirect association between co-exposure to tobacco and marijuana and infant behavior via poor growth at delivery."Furthermore, women who showed symptoms of anger, hostility and aggression reported more stress in pregnancy and were more likely to continue using tobacco and marijuana throughout pregnancy. Therefore, due to the co-exposure, they were more likely to give birth to infants smaller in size and who were more irritable and easily frustrated. The infants' irritability and frustration is also linked to mothers who experienced higher levels of stress while pregnant. "Our results suggest that interventions with women who smoke cigarettes or use marijuana while pregnant should also focus on reducing stress and helping them cope with negative emotions," Eiden says. "This may help reduce prenatal substance exposure and subsequent behavior problems in infants."

2018 Bolhuis et al studied maternal and paternal cannabis use during pregnancy and the psyvchotic-like experiences in the offspring. Abstract: Cannabis use continues to increase among pregnant women. Gestational cannabis exposure has been associated with various adverse outcomes. However, it remains unclear whether cannabis use during pregnancy increases the risk for offspring psychotic-like experiences. In this prospective cohort, we examined the relationship between parental cannabis use during pregnancy and offspring psychotic-like experiences. Comparisons were made between maternal and paternal cannabis

use during pregnancy to investigate causal influences of intra-uterine cannabis exposure during foetal neurodevelopmental. This study was embedded in the Generation R birth cohort and included N = 3692 participants. Maternal cannabis exposure was determined using self-reports and cannabis metabolite levels from urine. Paternal cannabis use during pregnancy was obtained by maternal report. Maternal cannabis use increased the risk of psychotic-like experiences in the offspring (ORadjusted = 1.38, 95% CI 1.03-1.85). Estimates were comparable for maternal cannabis use exclusively before pregnancy versus continued cannabis use during pregnancy. Paternal cannabis use was similarly associated with offspring psychotic-like experiences (ORadjusted = 1.44, 95% CI 1.14-1.82). We demonstrated that both maternal and paternal cannabis use were associated with more offspring psychotic-like experiences at age ten years. This may suggest that common aetiologies, rather than solely causal intra-uterine mechanisms, underlie the association between parental cannabis use and offspring psychotic-like experiences. These common backgrounds most likely reflect genetic vulnerabilities and shared familial mechanisms, shedding a potential new light on the debated causal path from cannabis use to psychotic-like phenomena. Our findings indicate that diagnostic screening and preventative measures need to be adapted for young people at risk for severe mental illness.

2018 Jansson et al looked at perinatal marijuana use and the developing child. Increasing public attention has recently been paid to the opioid epidemic and attendant effects on prenatally exposed infants and children.[1] Current literature has emerged proposing marijuana as a safe alternative to opioids in addressing pain[2] and cannabis legalization as a way to decrease opioid fatalities.[3] As a result, perceptions of cannabis safety have increased, and the prevalence of marijuana use among pregnant women has expanded; past-month cannabis use among pregnant US women increased from 2.4% to 3.9% between 2002 and 2014.[4] Further, cannabis potency has been substantially increasing over the past 4 decades in the United States, and will likely continue to do so as extraction procedures of active components improve.

2018 Bertrand et al investigated breast milk for cannabinoid concentrations. Abstract: Marijuana is the most commonly used recreational drug among breastfeeding women. With legalization of marijuana in several US states and a 1990 study in which authors documented psychomotor deficits in infants breastfed by mothers using marijuana, there is a need for information on potential exposure to the breastfed infant. Our objective with this study was to quantify cannabinoids in human milk after maternal marijuana use. Between 2014 and 2017, 50 breastfeeding women who reported marijuana use provided 54 breast milk samples to a research repository, Mommys Milk. Concentrations of Δ-9-tetrahydrocannabinol (Δ9-THC), 11-hydroxy-Δ-9-tetrahydrocannabinol, cannabidiol, and cannabinol were measured by using liquid chromatography mass spectrometry electrospray ionization. Δ9-THC was detectable in 34 (63%) of the 54 samples up to ∼6 days after last reported use; the median concentration of Δ9-THC was 9.47 ng/mL (range: 1.01‐323.00). Five samples had detectable levels of 11-hydroxy-Δ-9-tetrahydrocannabinol (range: 1.33‐12.80 ng/mL) or cannabidiol (range: 1.32‐8.56 ng/mL). The sample with the highest concentration of cannabidiol (8.56 ng/mL) did not have measurable Δ9-THC. Cannabinol was not detected in any samples. The number of hours since last use was a significant predictor of log Δ9-THC concentrations (−0.03; 95% confidence interval [CI] −0.04 to −0.01; *P* = .005). Adjusted for time since last use, the number of daily uses and time from sample collection to analysis were also significant predictors of log Δ9-THC concentrations (0.51; 95% CI 0.03 to 0.99; *P* = .039; 0.08; 95% CI 0.00 to 0.15; *P* = .038, respectively). Δ9-THC was measurable in a majority of breast milk samples up to ∼6 days after maternal marijuana use.

2018 Ryan et al conducted a review of marijuana use during pregnancy and breastfeeding and its implications for neonatal and childhood outcomes. Abstract: Marijuana is one of the most widely used substances during pregnancy in the United States. Emerging data on the ability of cannabinoids to cross the placenta and affect the development of the fetus raise concerns about both pregnancy outcomes and long-term consequences for the infant or child. Social media is used to tout the use of marijuana for severe nausea associated with pregnancy. Concerns have also been raised about marijuana use by breastfeeding mothers. With this clinical report, we provide data on the current rates of marijuana use among pregnant and lactating women, discuss what is known about the effects of marijuana on fetal development and later neuro-developmental and behavioral outcomes, and address implications for education and policy.

2018 Sokol et al looked at maternal cannabis use during a child's lifetime to see if it associated with earlier initiation. Abstract: Mother and child data were from the National Longitudinal Survey of Youth 1979 (1980-1998 waves) and Child and Young Adults (1988-2014 waves) cohorts, respectively. Cox proportional hazard models assessed the effect of maternal cannabis use prior to a child's adolescence on the child's risk of subsequent cannabis initiation. Models were stratified by race and child's age category (6-16, 17-24, ≥25 years). Adjusted analyses controlled for sociodemographic variables. Analyses were conducted in 2017. Median age of cannabis initiation for children of maternal ever users was age 16years

compared with age 18years among children of maternal never users. Children of 1-year and multiple-year users were at increased risk of cannabis initiation between ages 6 and 16years (hazard ratio=1.38, p<0.001, and hazard ratio = 1.45, p<0.001, respectively). Effects were slightly stronger among non-Hispanic non-black children. As cannabis legalization expands across the U.S., adult use may become increasingly normative. This study indicates that maternal cannabis use may be a risk factor for early initiation among their offspring. Preventive interventions should consider strategies to delay initiation among children of cannabis users.

2018 Murphy et al looked at Cannabinoid exposure and altered DNA methylation in rat and human sperm. Abstract: Little is known about the reproductive effects of paternal cannabis exposure. We evaluated associations between cannabis or tetrahydrocannabinol (THC) exposure and altered DNA methylation in sperm from humans and rats, respectively. DNA methylation, measured by reduced representation bisulfite sequencing, differed in the sperm of human users from non-users by at least 10% at 3,979 CpG sites. Pathway analyses indicated Hippo Signaling and Pathways in Cancer as enriched with altered genes (Bonferroni p<0.02). These same two pathways were also enriched with genes having altered methylation in sperm from THC-exposed versus vehicle-exposed rats (p<0.01). Data validity is supported by significant correlations between THC exposure levels in humans and methylation for 177 genes, and substantial overlap in THC target genes in rat sperm (this study) and genes previously reported as having altered methylation in the brain of rat offspring born to parents both exposed to THC during adolescence. In humans, cannabis use was also associated with significantly lower sperm concentration. Findings point to possible pre-conception paternal reproductive risks associated with cannabis use.

2019Young-Wolff et al Looked at self-reported daily, weekly and monthly cannabis use among women before and during pregnancy Abstract:. Cross-sectional study using data from 367 403 pregnancies among 276 991 women 11 years or older who completed a self-administered questionnaire on cannabis use during standard prenatal care in Kaiser Permanente Northern California from January 1, 2009, to December 31, 2017. The annual prevalence of self-reported daily, weekly, and monthly cannabis use among women before and during pregnancy was estimated using Poisson regression with a log link function, adjusting for sociodemographics. Data analyses were conducted from February to May 2019. EXPOSURES: Calendar year. MAIN OUTCOMES AND MEASURES: Self-reported frequency of cannabis use in the year before pregnancy and during pregnancy assessed as part of standard prenatal care (at approximately 8 weeks' gestation). RESULTS: Among the overall sample of 367 403 pregnancies among 276 991 women, 35.9% of the women self-reported white race/ethnicity; 28.0%, Hispanic; 16.6%, Asian; 6.0%, African American; and 13.5%, other. In the sample, 1.2% of the women were aged 11 to 17 years; 15.3%, 18 to 24 years; 61.4%, 25 to 34 years; and 22.0%, older than 34 years. Median (interquartile range) neighborhood household income was $70 472 ($51 583-$92 643). From 2009 to 2017, the adjusted prevalence of cannabis use in the year before pregnancy increased from 6.80% (95% CI, 6.42%-7.18%) to 12.50% (95% CI, 12.01%-12.99%), and the adjusted prevalence of cannabis use during pregnancy increased from 1.95% (95% CI, 1.78%-2.13%) to 3.38% (95% CI, 3.15%-3.60%). Annual relative rates of change in self-reported daily cannabis use (1.115; 95% CI, 1.103-1.128), weekly cannabis use (1.083; 95% CI, 1.071-1.095), and monthly or less cannabis use (1.050; 95% CI, 1.043-1.057) in the year before pregnancy increased significantly, with daily use increasing most rapidly (from 1.17% to 3.05%). Similarly, annual relative rates of change in self-reported daily cannabis use (1.110; 95% CI, 1.089-1.132), weekly cannabis use (1.075; 95% CI, 1.059-1.092) and monthly or less cannabis use (1.044; 95% CI, 1.032-1.057) during pregnancy increased significantly from 2009 to 2017, with daily use increasing most rapidly (from 0.28% to 0.69%). Results of this study demonstrate that frequency of cannabis use in the year before pregnancy and during pregnancy has increased in recent years among pregnant women in Northern California, potentially associated with increasing acceptance of cannabis use and decreasing perceptions of cannabis-associated harms.

2019 Petrangelo et al investigated cannabis abuse or dependence during pregnancy. Abstact: A retrospective population-based cohort of births in the United States between 1999 and 2013 was created using data from the National Inpatient Sample. Births to mothers who reported cannabis dependence or abuse were identified using ICD-9 codes, and the effect on various obstetrical and neonatal outcomes was assessed using logistic regression, adjusting for relevant confounders (Canadian Task Force Classification II-2). RESULTS:A total of 12 578 557 births were included in our analysis. The incidence of cannabis abuse or dependence rose from 3.22 in 1000 births in 1999 to 8.55 in 1000 births in 2013 (P < 0.0001). Women reporting cannabis dependence or abuse were more likely to have a preterm premature rupture of membranes (odds ratio [OR] 1.46; 95% confidence interval [CI] 1.35-1.58), a hospital stay of >7 days (OR 1.17; 95% CI 1.11-1.23), and an intrauterine fetal demise (OR 1.50; 95% CI 1.39-1.62). Neonates born to exposed mothers had a higher risk of prematurity (OR 1.40; 95% CI 1.36-1.43) and growth restriction (OR 1.35; 95% CI 1.30-1.41). CONCLUSION: Cannabis use during pregnancy steadily increased over the study

period. Users of cannabis during gestation were more likely to have adverse outcomes during delivery and require longer periods of hospitalization. Neonates born to exposed mothers were more likely to be born preterm and underweight.

2019 Corsi et al looked at the association between self-reported prenatal cannabis use and maternal, perinatal and neonatal outcomes. Population-based retrospective cohort study covering live births and stillbirths among women aged 15 years and older in Ontario, Canada, between April 2012 and December 2017. EXPOSURES: Self-reported cannabis exposure in pregnancy was ascertained through routine perinatal care.MAIN OUTCOMES AND MEASURES: The primary outcome was preterm birth before 37 weeks' gestation. Indicators were defined for birth occurring at 34 to 36 6/7 weeks' gestation (late preterm), 32 to 33 6/7 weeks' gestation, 28 to 31 6/7 weeks' gestation, and less than 28 weeks' gestation (very preterm birth). Ten secondary outcomes were examined including small for gestational age, placental abruption, transfer to neonatal intensive care, and 5-minute Apgar score. Coarsened exact matching techniques and Poisson regression models were used to estimate the risk difference (RD) and relative risk (RR) of outcomes associated with cannabis exposure and control for confounding. RESULTS:In a cohort of 661 617 women, the mean gestational age was 39.3 weeks and 51% of infants were male. Mothers had a mean age of 30.4 years and 9427 (1.4%) reported cannabis use during pregnancy. Imbalance in measured maternal obstetrical and sociodemographic characteristics between reported cannabis users and nonusers was attenuated using matching, yielding a sample of 5639 reported users and 92 873 nonusers. The crude rate of preterm birth less than 37 weeks' gestation was 6.1% among women who did not report cannabis use and 12.0% among those reporting use in the unmatched cohort (RD, 5.88% [95% CI, 5.22%-6.54%]). In the matched cohort, reported cannabis exposure was significantly associated with an RD of 2.98% (95% CI, 2.63%-3.34%) and an RR of 1.41 (95% CI, 1.36-1.47) for preterm birth. Compared with no reported use, cannabis exposure was significantly associated with greater frequency of small for gestational age (third percentile, 6.1% vs 4.0%; RR, 1.53 [95% CI, 1.45-1.61]), placental abruption (1.6% vs 0.9%; RR, 1.72 [95% CI, 1.54-1.92]), transfer to neonatal intensive care (19.3% vs 13.8%; RR, 1.40 [95% CI, 1.36-1.44]), and 5-minute Apgar score less than 4 (1.1% vs 0.9%; RR, 1.28 [95% CI, 1.13-1.45]). CONCLUSIONS AND RELEVANCE:Among pregnant women in Ontario, Canada, reported cannabis use was significantly associated with an increased risk of preterm birth. Findings may be limited by residual confounding.

2019 Schrott et al found a gene linked to autism which undergoes changes in men's sperm after pot use. A specific gene associated with autism appears to undergo changes in the sperm of men who use marijuana, according to new research. The gene change occurs through a process called DNA methylation, and it could potentially be passed along to offspring.

2019 Fish et al investigated whether CBD, THC use during early pregnancy can disrpt fetal development. We tested whether cannabinoids (CBs) potentiate alcohol-induced birth defects in mice and zebrafish, and explored the underlying pathogenic mechanisms on Sonic Hedgehog (Shh) signaling. The CBs, Δ9-THC, cannabidiol, HU-210, and CP 55,940 caused alcohol-like effects on craniofacial and brain development, phenocopying Shh mutations. Combined exposure to even low doses of alcohol with THC, HU-210, or CP 55,940 caused a greater incidence of birth defects, particularly of the eyes, than did either treatment alone. Consistent with the hypothesis that these defects are caused by deficient Shh, we found that CBs reduced Shh signaling by inhibiting Smoothened (Smo), while *Shh* mRNA or a CB1 receptor antagonist attenuated CB-induced birth defects. Proximity ligation experiments identified novel CB1-Smo heteromers, suggesting allosteric CB1-Smo interactions. In addition to raising concerns about the safety of cannabinoid and alcohol exposure during early embryonic development, this study establishes a novel link between two distinct signaling pathways and has widespread implications for development, as well as diseases such as addiction and cancer.

2020 Skelton et al investigated recreational cannabis legalisation in the US and maternal use during the preconception, prenatal and postpartum periods. Abstract: In the United States (US), recreational cannabis use is on the rise. Since 2011, 11 states and the District of Columbia have legalized cannabis for adult recreational use. As additional states consider legalizing, there is an urgent need to assess associations between recreational cannabis legalization and maternal use in the preconception, prenatal, and postpartum periods—all critical windows for maternal and child health. Using cross-sectional data from the 2016 Pregnancy Risk Assessment Monitoring System, we assessed associations between state cannabis legalization and self-reported maternal cannabis use. Using logistic regression, we estimated the adjusted prevalence ratio (PR) of cannabis use during the preconception, prenatal, and postpartum period for women delivering a live-born infant in three states that had legalized recreational cannabis (Alaska, Colorado, and Washington) and three states that had not legalized (Maine, Michigan, and New Hampshire) by 2016. Our final sample size was 7258 women. We utilized 95% confidence intervals (CI) and a significance level of *alpha* = 0.05. After adjustment for potential confounders, women who resided in states with legalized

recreational cannabis were significantly more likely to use cannabis during the preconception (PR 1.52; 95%CI ranging from 1.28–1.80; $p < 0.001$), prenatal (PR 2.21; 95% CI ranging from 1.67–2.94; $p < 0.001$), and postpartum (PR 1.73; 95%CI ranging from 1.30–2.30; $p < 0.001$) periods, compared to women who resided in states without legalized recreational cannabis. Although evidence about the effect of marijuana use during these periods is nascent, these findings show potential for increased incidence of child exposure to cannabis. Longitudinal research is needed to assess immediate and sustained impacts of maternal use before and after state legalization of recreational cannabis.

2020 Slotkin et al Looked at paternal tHC exposure prior to mating and found that in elicits deficits in cholinergic synaptic function in the offspring. Little attention has been paid to the potential impact of paternal marijuana use on offspring brain development. We administered Δ9-tetrahydrocannabinol (THC, 0, 2, or 4 mg/kg/day) to male rats for 28 days. Two days after the last THC treatment, the males were mated to drug-naïve females. We then assessed the impact on development of acetylcholine (ACh) systems in the offspring, encompassing the period from the onset of adolescence (postnatal day 30) through middle age (postnatal day 150), and including brain regions encompassing the majority of ACh terminals and cell bodies. Δ9-Tetrahydrocannabinol produced a dose-dependent deficit in hemicholinium-3 binding, an index of presynaptic ACh activity, superimposed on regionally selective increases in choline acetyltransferase activity, a biomarker for numbers of ACh terminals. The combined effects produced a persistent decrement in the hemicholinium-3/choline acetyltransferase ratio, an index of impulse activity per nerve terminal. At the low THC dose, the decreased presynaptic activity was partially compensated by upregulation of nicotinic ACh receptors, whereas at the high dose, receptors were subnormal, an effect that would exacerbate the presynaptic defect. Superimposed on these effects, either dose of THC also accelerated the age-related decline in nicotinic ACh receptors. Our studies provide evidence for adverse effects of paternal THC administration on neurodevelopment in the offspring and further demonstrate that adverse impacts of drug exposure on brain development are not limited to effects mediated by the embryonic or fetal chemical environment, but rather that vulnerability is engendered by exposures occurring prior to conception, involving the father as well as the mother.

2020 Mark et al looked at pregnant women's current and intended cannabis use in relation to their views toward legalization and knowledge of potential harm. Abstract: **Objectives:** The objective of this study was to investigate pregnant women's current use of cannabis and their intended patterns of use with relation to their views on the legalization of cannabis and their knowledge of potential harms. **Methods:** A voluntary, anonymous survey regarding patterns of use of cannabis and views on legalization was distributed to a convenience sample of pregnant women presenting for prenatal care at an outpatient university clinic. Chi-square and Fischer's exact tests were used for analysis using STATA. **Results:** Of 306 surveys returned, 35% of women reported currently using cannabis at the time of diagnosis of pregnancy and 34% of those women continued to use. Seventy percent of respondents endorsed the belief that cannabis could be harmful to a pregnancy. Fifty-nine percent of respondents believed that cannabis should be legalized in some form and 10% reported that they would use cannabis more during pregnancy if it were legalized. Those who continued to use cannabis during pregnancy were less likely than those who quit to believe that cannabis use could be harmful during pregnancy (26% vs 75%, $P < 0.001$). The most common motivation for quitting cannabis use in pregnancy was to avoid being a bad example (74%); in comparison, only 27% of respondents listed a doctor's recommendation as a motivation to quit. **Conclusions:** Cannabis use during pregnancy is relatively common and persistent, despite knowledge of the potential risks of harm. Views toward legalization vary among pregnant women and may impact cannabis use during pregnancy. In a changing legal climate, there is a need for clear messaging on the effects of cannabis use during pregnancy.

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Effects of Cannabis on cognitive functioning, personality and educational performance.

In 1986 two wide-ranging review studies were carried out of all the papers into cognitive functioning and cannabis up to that time. The results were inconclusive. However it was suggested that the differential impairment observed in subjects - some users suffered damage while others did not under identical conditions, may be because of a differential vulnerability of the subjects: for example, some may be more susceptible to cerebral impairment (Wert and Raulin 1986). This suggestion has now been accepted in general for many illnesses. It should be pointed out that, the American market was at that time still dominated by weaker preparations of cannabis.

Since then, testing methods have become more sensitive and cannabis damage has been found to be subtler than expected and of a different type from that caused by alcohol.

Renewed testing of some of the older studies, with more sophisticated techniques, found definite differences between users and non-users especially in the fields of sustained attention and short-term memory (Page et al 1988).

The following experiments were normally carried out at least 24 hours after abstention from cannabis to get rid of the intoxicating effects.

Block and others (1990) found that intense prolonged use of cannabis impairs the ability to express oneself verbally and to solve maths problems.

Schwartz et al (1989) in a study of teenagers using 7% THC long-term (It was already in the USA in the late eighties), showed significant impairment of short-term memory, persisting for at least 6 weeks after stopping. Unfortunately the money then ran out.

Prolonged use of marijuana lessens the ability to focus attention and screen out irrelevant information (Solowij 1991,1995a, 1995b) In 1999 she reported that this held true even after abstention for 2 years. She also found a direct relationship between the degree of impairment and length of time of abuse.

Sixty-five heavy users of cannabis (smoking every day) male and female, were compared with sixty-four "light" users (median of one/day in the last 30 days). After abstention for a minimum of 19 hours, the heavy users had significantly greater impairment than the light ones on attention and executive functions (decreasing mental flexibility and reduced learning ability) after adjustment for confounding factors (Pope et al 1996).

Hall and others (1994), Lundqvist (1995), Leavitt et al and various other researchers all reported that long-term cannabis produces the following effects:

"impaired ability to carry out complex thought operations and impaired ability to screen out distracting impressions;
reduced ability to process information;
no effect on long-term memory but impaired short-term memory, particularly with regard to information which is of a kind unfamiliar to the individual or which is complex in nature;
difficulty in carrying out tasks which require intellectual flexibility, long-term strategic planning and the ability to learn from experience;
no effect on the ability to deal with the routine, familiar demands of everyday life, but problems when faced with the task of expressing oneself verbally in a new, unfamiliar situation or in a situation where old ways of thinking and old knowledge are inadequate" (in Ramstrom 2003).

Dr Thomas Lundqvist of Lund University Hospital, Sweden, is one of the researchers who has contributed most to this aspect of cannabis use. In his PhD thesis in 1995 he studied the cognitive damage acquired by some 400 of the long-term cannabis abusers who had sought treatment at his outpatient clinic. His clinical observations provide a wealth of information about the various effects of cannabis. He divided the cognitive functions impaired into 7 different categories.
A summary of his findings can be found in *"Adverse Health Consequences of Cannabis Use: A Survey of Scientific Studies Published up to and including the Autumn of 2003"* by Jan Ramstrom as follows:

Verbal Ability
Having a vocabulary that corresponds to one's age, finding the words for what one wants to say, understanding others and having the ability for abstract thought.
Logical-analytical ability
Ability to analyse and draw logical conclusions. Ability to understand causal connections and ability to judge oneself in a critical/logical manner.
Psychomotility
Ability to maintain attention and to vary the degree and focus of attention. Ability to understand other points of view and to change one's own point of view. Some degree of general flexibility with regard to different ways of looking at and interpreting societal phenomena.
Memory
Short-term memory/working memory: Ability to remember what has just happened or been communicated, which is a prerequisite not only for the integration of what has just been communicated but also for the integration and organisation of a whole range of cognitive processes, as well as a precondition for a reasonably adequate temporal perception
Long-term memory: This consists of both "episodic memory", which makes it possible to remember events and their temporal context. And "semantic memory", which has more to do with what we call "knowledge", e. g. different facts and the inter-relationships between different phenomena.
Analytical and synthetic ability
Based on the ability to combine the other functions. Makes it possible to synthesise, sort out and organise mental material.
Psychospatial ability
Makes it possible to orientate oneself, other people and various phenomena in time and space, which is a precondition for temporal organisation as well as one of the prerequisites for social orientation.
Gestalt memory (holistic memory)
Enables us to understand and form patterns – not only to understand that there is a connection, but also to understand its nature and structure. For example, enables us to make and maintain the connection between a person, a name and a social role.

He found more or less pronounced weaknesses in all categories for all 400 subjects. Lundqvist also described a personality profile which he said was typical of cannabis users:

'Have difficulty in finding the words to express what they really mean.
Have a limited ability to be amused by or enjoy literature, film, theatre or the like.
Have a feeling of boredom and emptiness in everyday life, along with feelings of loneliness and of not being understood.
Externalise problems and are unable to take criticism.
Are convinced that they are functioning adequately.
Are unable to examine their own behaviour self-critically.
Feel that they have low capacity and are unsuccessful.
Are unable to carry on a dialogue.
Experience difficulty in concentrating and paying attention.
Have rigid (fixed) opinions and answers to questions.
Make statements such as "I'm different, other people don't understand me, I don't belong to society".
Do not plan their day.
Think they are active because they have many on-going projects - which they seldom see through to completion.
Have no daily or weekly routines'.

Ten former cannabis abusers were interviewed between 2 and 10 months after they had stopped concerning any changes they had experienced. All said their way of thinking and their perception of the world had changed. Most importantly they said their verbal ability, logical analytical ability and psychomotility had got better.

Nearly 10 years before, Hendin and others (1987) had asked 150 white long-term (6 days/week for at least 2 years) cannabis users subjective questions regarding their habit and its effects on them. No alcohol or other drugs were used by them, nor were they socially disadvantaged or marginalised in any way. Two thirds felt their main problem was one of memory impairment. Just under half said their ability to concentrate on a complex task had worsened and the same number couldn't finish jobs. Just over 40% considered their ability to think was less clear and 36% were less ambitious.

Cannabis users often claim that the drug gives them insight, increases self-awareness and gives them a deeper understanding of life. Many of the researchers were struck by the consistency of exactly the opposite results. Introspection was inhibited, thoughts and feelings were separated and individuals were less able to distinguish what is reality.

Obviously a reduction in memory capability will impact on learning ability and should be cause for concern especially with regard to our children. Exposure to drugs and vulnerability from them is at its highest in the teenage years. A paper on the development of the brain by Giedd (1999) points out that the brain is still maturing into the mid-twenties and Chambers and others (2003) say that the motivation/risk taking areas of the brain develop faster than the parts responsible for inhibition. Charles Nelson, a child psychologist from The University of Minnesota said, "Adolescents are capable of very strong emotions and very strong passions but their pre-frontal cortex hasn't caught up with them yet. It's as though they don't have the brakes that allow them to slow these emotions down". Another study into the effects of marijuana on morphological changes in the brain in 2000 (Wilson et al), found that the age at which marijuana exposure begins is important. Subjects who started to use marijuana before the age of 17 were compared with those who began later. The younger starters had smaller whole brain and percent cortical grey matter and larger percent white matter volumes, the males had significantly higher CBF (Cerebral Blood Flow) than other males. Both sexes who started younger were physically smaller in height and weight.

Adolescents are minors and their decisions to use or not use drugs are not conventionally regarded as being as free and informed as in the case of choice for adults (Kleiman1989).
If a child uses cannabis regularly during the transition period from childhood to adulthood, then educational achievement, becoming independent from parents, relationships including marriage and career choice, all these processes may be expected to be affected (Baumrind and Moselle 1985, Polich, Ellickson, Reuter and Kahan, 1984). The possible excalating use of cannabis and progression to the use of other drugs, not to mention the risk of accidents especially while driving should all be causes for concern (Kleiman 1989, Polich, Ellickson, Reuter and Kahan, 1984).

A clinic in Sweden, The Maria Ungdomsmottagning in Stockholm, finds it often easier to give help to young people dependent on heroin than to firmly addicted cannabis users (Ramstrom 2003). Parents' associations in Sweden and the USA, campaigning against drugs, take a very strong anti-cannabis position as they have witnessed numerous cases of the development of teenagers come to an abrupt stop because of its use (Ramstrom 2003).

Baumrind and Moselle (1985) said the forging of a personal identity is central to the maturing of children and Ramstrom in 1991 emphasised the importance of social integration to develop identity in the later teenage years. The ability for abstract thought is also crucial for forging an identity (Baumrind and Moselle 1985, Ramstrom 1991 and Steingart 1969).

The ability to perform formal thought operations is the basis of the ability for abstract thought – the vision of a world differing from reality. This skill also provides the foundation for long-term planning of the development of one's own personality. For example a child may say, "When I grow up I'll be a doctor". This should be replaced by a statement reflecting an increasingly maturing adolescent, "If I work hard, choose the right subjects and get good grades, I will be able to apply to medical school"(Lundqvist 1995).

Ramstrom (2003) said, "If the development of identity does not progress, the teenager remains at a childish level of development characterised by both a lack of independence and a deficient integration in the adult world". He also said, " Deterioration of short-term memory obviously makes learning more difficult, but it also has a negative effect on the individual's ability to make plans, to establish new relationships and to make realistic assessments of the world around him or her".

Kerstin Tunving wrote in an article in 1987, "To sum up, the impression is, based on clinical observations, that teenagers who abuse cannabis "sleep away" their teens. They often do not develop at the same pace as youth of the same age, but stay childish and dependent".

In recent years, researchers have found associations between cannabis use and mental and social problems in the late teens and early adulthood, psychosis (Arsenault 2002) depression and suicidal thoughts (Bovassa 2001 and Patton et al 2002), crime and unemployment (Fergusson and Horwood 1997, Fergusson et al 2000, 2002).

Detailed descriptions of the long-term effects of cannabis use on teenagers is present in textbooks, Heinemann 1984, Ranstrom 1987, Lunqvist report 1995, and in a paper by Kolansky and Moore 1971.

Holmberg (1981) studied over 1000 Swedish 15 to 16 year olds, with a follow up 11 years later. The following results were found:
Mortality rates were 5 to 8 times higher among the original abusers. They also had experienced more medical and social problems, 10% had had a psychotic episode during the time and the 2.4% who were heavy users were more likely to have become properly addicted.

A very extensive longitudinal in-depth study of young cannabis users was carried out by Newcombe and Bentler in 1988. It focused on the transition to adulthood. Not surprisingly the risk of impairment to mental functions increased, they were less able to make careful plans, had negative psychosocial factors in the teenage years and were more likely to drop out of school or training courses. They found it harder to hold down a job, experienced more divorces and had worse social networks.

Confirmation of these findings came from Fergusson and his co-workers in 1997, 2000 and 2002 (Christchurch Study). They said, "Cannabis use, and particularly regular or heavy use, was associated with increased rates of a range of adjustment problems in adolescence/young adulthood – other illicit drug use, crime, depression, and suicidal behaviours – with these adverse effects being most evident for school aged regular users".

It has already been mentioned that cannabis use can impair memory, attention and therefore learning (Baumrind and Moselle 1985), thus potentially increasing the risk of high school failure and possible drop-out. These findings were supported in cross-sectional studies by Kandel (1984), Robins and others 1970, and Hawkins and others in 1992. They all found a positive relationship with cannabis use as an adult and the risk of dropout from school.

Longitudinal studies by Kandel in 1986 and Newcombe and Bentler 1988, however, gave mixed support for the idea. Kandel looked at her cross-sectional study again and reported that the connection all but disappeared as the dropout students using cannabis had lower aspirations than the controls. Newcombe and Bentler found only a negative effect of *hard drugs* in adolescence and completion of high school.

More recently, Lynskey and Hall conducted a review of papers on educational attainment in 2000. They concluded that cannabis use significantly increases the risk of poor school performance and early school leaving.

To quote, "Cross-sectional studies have revealed significant associations between cannabis use and a range of measures of educational performance including lower grade point average, less satisfaction with school, negative attitudes towards school, increased rates of absenteeism and poor school performance…… A number of prospective longitudinal studies have indicated that early cannabis use may signify increased risks of subsequent poor performance and in particular, early school leaving. This association has remained after control for a wide range of prospectively assessed co-variables…….In particular , early cannabis use appears to be associated with the adoption of an anti-conventional lifestyle characterised by affiliations with delinquents and substance-using peers, and the precocious adoption of adult roles including early school leaving, leaving the parental home and early parenthood".

The survey proposed that the link between early cannabis use and educational attainment arises because of the social context within which cannabis is used and not because cannabis use causes impairment. However Solowij (1998) concluded there is evidence that long-term cannabis use (daily or near-daily for 10 years or more), was associated with the impairment of selective attention. Few adolescents will have used cannabis intensively or for long enough to produce the effects seen in adults.

Hall added that this does not mean that acute cognitive impairment is irrelevant in adolescents, only that cognitive impairment found in those who use cannabis is more likely to be the results of acute intoxication than the effects of long-term use. If adolescents used regularly then school performance would suffer especially if they were poor or average to start with.

Solowij also said (1998) in her book "Cannabis and Cognitive Functioning", "Use more often than twice per week for even a short period of time, or use for 5 years or more at the level of even once per month, may each lead to a compromised ability to function to their full mental capacity, and could possibly result in lasting impairments (this does not imply that use below these levels may be considered safe)".

I can certainly concur with these findings. I have seen the performance of a few of my students, bright grammar school boys, slowly deteriorate. They fail to achieve the grades they deserve and some miss out on the university of their choice. They will never admit to using cannabis, the information often comes from their peers, and some parents simply do not want to know.

In another paper in 2001 Hall said that it is clear that heavy cannabis use may compromise educational attainment and thus future achievement.

Two papers in 2002 added to the evidence. One by Solowij et al examined the effects of the duration of cannabis use on specified areas of cognitive functioning among users seeking treatment for cannabis dependence. Their results confirmed that long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use. And Bolla and colleagues also found heavy cannabis use to be associated with persistent decrements in neurocognitive performance even after 28 days of abstention. They said it was unclear if these decrements would resolve with continued abstinence or grow progressively worse with continued heavy marijuana use.

The preliminary results of a longitudinal study into the effects of marijuana use on IQ in The Canadian Medical Association Journal (2002), reported that current use of the drug had a negative effect on global IQ scores only in subjects who smoked 5 or more joints a week. It was not found in previously heavy users who had now given up so did not have a long-term impact. IQs were tested in 9 to 12 year olds and again when they reached 17 to 20. The drop was around 4 points.

In 2003 Pope and others found early-onset cannabis users exhibiting poorer cognitive performance than late-onset users or control subjects especially in verbal IQ, but they could not determine the cause of this difference from their data.

Fergusson, Horwood and Beautrais in 2003 found an increased cannabis use to be associated with an increase in school leaving, qualifications, failure to enter university and failure to obtain a university degree. This connection persisted after control for confounding factors. There was no evidence to suggest the presence of reverse causal pathways, i.e. that lower educational achievement lead to increased cannabis use. The findings support the view that cannabis use may act to decrease educational achievements in young people. It is likely that this reflects the effects of the social context within which cannabis is used rather than any direct effect of cannabis use on cognitive ability or motivation.

Lynskey and others in 2003 published the results of another study of high school completion. They concluded: “Early regular cannabis use (weekly use at age 15), is associated with an increased risk of leaving school early”. And Bray and others in 2000 said a teenage marijuana user’s odds of dropping out are more than twice that of a non-user.

The National Household Survey on Drug Abuse in America in 2002 reported that marijuana use is linked to poorer grades. A teenager with an average “D” grade is 4 times more likely to have used marijuana than a teenager with an average “A” grade.

Professor Robin Murray, Director of The Institute of Psychiatry in London, was quoted in The Times on Saturday 12th February 2005, “ One of the reasons why some young people who smoke cannabis start performing badly at school or university is that they are cognitively impaired by the cannabis lingering in their brain. A young person who smokes cannabis every day, or even 3 times a week, can be in a state of low-grade intoxication most of the time. However, if you stop, these adverse cognitive effects also stop”.

The most recent evidence on cannabis and cognitive functioning comes from Greece and a study by Messinis and some of his colleagues (March 2006). They concluded that long-term marijuana use is linked to “subtle deficits in specific neuropsychological domains”. Those who smoked at least 4 joints a week for several years performed significantly worse than non-users. In particular, verbal learning (the ability to remember previously learned words) and executive functioning (organising and coordinating simple tasks), were among the worst affected.

Wadsworth and others in January 2006 aimed to examine whether an association existed between cannabis use, cognitive performance, mood, and human error at work. There was a positive relation between cannabis use and impairment of cognitive functioning and mood. No more errors were reported in the

workplace than in the controls. There was also a positive correlation with lower alertness and a slower response in organising things. Memory problems were evident at the start of the week and psychomotor slowing and poorer recall of episodes at the end of the week.

Ranganathan and D'Souza in 2006 reviewed the literature on the acute effects of cannabinoids on memory tasks in humans. Their conclusion suggested that cannabinoids impair all stages of memory including encoding, consolidation and retrieval.

In contrast to other research findings, Dr Igor Grant, editor of the Journal of The International Neuropsychological Society which he founded, wrote in the July 2003 edition that marijuana smoking has only a marginally harmful long-term effect on learning and memory. No effect at all was seen on other functions including reaction times, attention, language, reasoning ability and perceptual and motor skills. Dr Grant said he found the findings to be of particular significance since several states are considering whether to make it available as a medicinal drug. The paper was sponsored by a state-supported programme to oversee research into the use of cannabis to treat certain diseases. (Dr Grant is Director of The University of California Center for Medicinal Cannabis Research).

Dr Thomas Lundqvist in a review of the cognitive consequences of cannabis use in 2005 documented studies into the subject using brain-imaging techniques to try to reveal any neurotoxic effects of cannabis. Neuro-imaging data has been extracted from studies on acute and chronic abusers of marijuana in resting and in challenging cognitive situations.

Several studies at rest, using different techniques CBF, PET, SPECT, fMRI showed sub-normal cerebral blood flow or lower cerebellar metabolism in long-term users assessed within one week of abstention. Marijuana users showed 9% lower values of average whole brain activity compared with controls. Also at rest, acute exposure to marijuana gave rise to increases in dose-related CBF (Cerebral Blood Flow) in experienced users in some areas of the brain but not others e.g. those that are memory related.

When given a cognitive challenge, the controls showed significant activation in the pre-frontal cortex. Heavy smokers 24 hour to 28 days after washout, dislplayed diminished activity in this region but increased activity in another (the cingulate) which was not seen in the controls. There is thus a differential of cortical activity in subjects with a history of heavy cannabis use. CBF was decreased in areas associated with attention and attentional moderation of sensory processing.

In one study using PET scans, following a 25 day abstention, heavy users had no deficit in their executive functioning, at the same time as showing hypo-activity in some of the areas responsible for executive functioning and hyperactivity in others. This suggests there may be an alternative neural network employed as compensation i.e. they "work harder" to meet the demands of the task.

Lundqvist concluded that neuropsychological and brain-imaging techniques point to deficits in attention, memory and executive functioning.

He also suggested that studies failing to detect cognitive decline associated with cannabis use may reflect insufficient heavy or chronic use of cannabis in the sample or use of insensitive assessment instruments.

Herning and others (2005) also proposed a "blood flow theory" to account for the deficits in cognitive functioning among users of cannabis. Using Transcranial Doppler Sonography they recorded blood flow velocity in the cerebral arteries of heavy, moderate and light users, 3 days after admission to an in-patient research unit and after 28 to 30 days of monitored abstention. The conclusion was that "Chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated in part, in blood vessels or in the brain parenchyma. These findings might provide a partial explanation for the cognitive deficits observed in a similar group of marijuana users".

Marijuana's well-known effects on memory (short-term) according to neuroscientists, may be the result of misfiring brain cells. A paper published on 19th November 2006 by Robbe and others found that rats given THC experienced disruptions in the synchronous brain-cell firing that causes the formation of memories. There was a slowing of brain wave activity, principally theta and fast-ripple waves (believed to be involved in short-term memory formation) but also gamma waves (thought to help in moving memories into long-term storage). At very high doses the drug appeared to prevent learning altogether.

Chronic abuse of different drugs cause similar brain changes. Whether long-term users favour cocaine, cannabis or PCP, autopsies of their brains show a number of common gene changes consistent with diminished brain plasticity (ability to learn from new experiences and adapt to new situations). A paper by Lehrmann and others found that the anterior pre-frontal cortex (decision-making region) was dysfunctional in the brains of drug users. The brains of 42 deceased abusers were studied. Nearly 80% of them had similar alterations in genetic output compared to the controls. Genes involved in calcium signalling were turned down and those in lipid and cholesterol-related pathways were turned up. The abuser's ability to make sound decisions could be threatened.

An Australian study by George Patton et al 2007, on nearly 2000 Victorian high school 14 to 15 year olds since 1992 has found that, "while both alcohol and cannabis carried health risks, the overwhelming evidence was that cannabis was "the drug for life's future losers". Almost two thirds had tried cannabis before they were 18. They are more likely to suffer poor long-term mental health than drinkers, more likely to graduate to amphetamines, ecstasy and cocaine, and be less likely to be working, be qualified or in a relationship. They concluded, "Heavier teenage cannabis users tend to continue selectively with cannabis use. Considering their poor young adult outcomes, regular adolescent cannabis users appear to be on a problematic trajectory".

Jan Van Ours and Jenny Williams wrote a discussion paper in September 2007 about cannabis and educational attainment. People between 25 and 50 were interviewed. Those initiated into cannabis use earliest suffer the greatest adverse effects. Future earnings and prospects are both damaged. They concluded that, "1. Preventing cannabis uptake will improve the educational outcomes of youths, and 2. even if cannabis use cannot be prevented, delaying the age at which uptake occur will deliver educational benefits".

A paper in 2008 by Quinn et al found that adolescent rats were less averse to repeated doses of THC than adult rats but had greater residual cognitive deficits andd changes in hippocampal protein expression. The dose mimicked that of heavy cannabis use in humans. The adults after 2 weeks avoided the region of the cage associated with injections but the youngsters didn't. Many more protein changes were found in the adolescents and they had trouble with short-term memory. It was pointed out that the brains of the young rats were not yet fully developed so they were more vulnerable.

In 2008 Fegusson updated his findings from the Christchurch Study. He found, " …increasing cannabis use in late adolescence and early adulthood is associated with a range of adverse outcomes later in life. High levels of cannabis use are related to poor educational outcomes, lower income, greater welfare dependence and unemployment and lower relationship and life satisfaction".

2008 Perkonigg et al found that youth cannabis use commonly extends into adulthood. Over 3000 (14 to 24 years old) German youg people were followed. Of those who had repeated use of cannabis at baseline, 56% were still using it 4 years later and 46% 10 years later.

2008 Caldeira et al found that first year college students show high rate of cannabis use disorders. In a group of students who had used cannabis more than 5 times in the past year, 1 in 10 met the criteria for dependence and 14.5% met the criteria for cannabis abuse. 474 participants had used cannabis more than 5 times and of those: 24.3% regularly put themselves in physical danger when under the influence; 10.6% continued to use despite problems with family or friends; 40.1% reported concentration problems and 13.9% said they missed classes.

2008 Jager and Ramsey looked at long-trm consequences of adolescent marijuana use on the development of cognition, brain structure and function in an overview. They concluded: Over the last decade there has been a steady increase in the prevalence of frequent cannabis use among teenagers, accompanied by a decrease in age of first use. Evidence from both animal and human studies suggests that the severity of the effects of cannabis use on cognitive development is dependent on the age when cannabis use begins. One possible explanation is that those who begin cannabis use early in adolescence are more likely to become heavily dependent. It is plausible that chronic cannabis abuse will then interfere with educational and vocational training. From a more biological perspective, however, use of cannabis during critical developmental periods in the still maturing brain may induce persistent alterations in brain structure and brain function. Therefore, the effects of frequent cannabis use during adolescence could be different from and more serious than during adulthood, an issue increasingly recognized in the field of cannabis research. In this paper we review the relevant animal and human literature on long-term effects of frequent exposure

to cannabis during adolescence on the development of cognition, brain structure and function, and discuss implications, methodological and conceptual issues, and future prospects.

Yucei, Solowij et al 2008, performed high-resolution structural magnetic resonance imaging on 15 men (average age 39.8 years) who smoked more than 5 joints/day for 10 years, and compared them with images from 16 individuals (Average age 36.4 years) who were not cannabis users. The hippocampus (memory and emotion) and the amygdala (fear and aggression) tended to be lower in cannabis users, by 12% and 7.1% respectively. They concluded, " Although modest use may not lead to significant neurotoxic effects, these results suggest that heavy use might indeed be toxic to human brain tissue".

Ashtari and others in 2009 discovered that the developing brains of teens may be disrupted by heavy marijuana use. They used DTI (Diffusion Tensor Imaging) in 14 heavy smokers (Averaging nearly 6 joints/day in the final year of their smoking (they had smoked from 13 to 18/19 years of age). Abnormalities were seen in areas connecting memory, decision-making, attention, language and executive functioning skills – exactly the critical areas which develop in late adolescence. The images suggested damage or an arrest in developmentof the myelin sheath (insulation) that surrounds brain fibres. This abnormal white matter development could slow down information transfer and affect cognitive functioning. Five of the subjects also had a history of alcohol abuse.
Gobbi et al 2009, discovered that daily consumption of cannabis in teens can cause depression and anxiety and have irreversible long-term effects ont the brain. 'Teenagers who are exposed to cannabis have decreased serotonin transmission which leads to mood disorders as wel as increased norepinephrine transmission which leads to greater long-term susceptibility to stress', she said. Damage caused is more serious during adolescence than adulthood.

2009 Hester et al in 2009, using brain-imaging technology showed that during a decision game, chronic marijuana users showed less activity in an error-processing part of the brain than peers who do not use. They did not make more mistakes than the controls but were significantly less likely to realise it they had done 91% compared with 77%. This deficit in awareness may contribute to their continued use of the drug.

2009 Rubino et al looked at changes in hippocampal morphology induced by adolescent HC treatment. THC Pretreated rats had a significantly lower total dendritic length and number than vehicles, as well as reduced spine density. Our data suggest that THC pretreated rats may establish less synaptic contacts and/or less efficient synaptic connections throughout the hippocampus and this could represent the molecular underpinning of the cognitive deficit induced by adolescent THC treatment.

2010 A study from Australia by Degenhardt et al found that occasional cannabis use in adolescence predicts later drug use and educational problems. Nearly 2000 secondary school pupils were followed from 14.9 to 24 years of age. Those who continued cannabis use into early adulthood had higher risks of later adult alcohol and tobacco dependency and illicit drug use., as well as being less likely to complete a post secondary qualification.

2010 Dumontheil and others found that lack of concentration in adolescents is to do with brain structure, their mental capacities are not the same as adults. They found an unexpected level of activity in the prefrontal cortex which is involved in multi-tasking and decision-making. This means it continues to do a lot of needless work when making decisions. This "chaos" continues till the late 20s. These chaotic thought patterns are a result of too much grey matter. As we age the amount of grey matter decreases.

2010 November Staci Ann Gruber, speaking at Neuroscience 2010, the annual meeting of The Society of Neuroscience reported that people who start using marijuana at a young age have greater cognitive shortfalls. Researchers also found that the more marijuana a person used corresponded to greater difficulties in focus and attention. (Teen's brains are only about 80% developed and are not completed till the 20s or 30s).

2010 Demirakca T et al discovered diminished gray matter in the hippocampus of cannabis users. Chronic cannabis use has been associated with memory deficits and e reduction in volume of the hippocampus, but no study yet has accounted for the different effects of THC and CBD. Cannabis users showed lower GM (gray matter) volumes located in a cluster of the right anterior hippocampus. An inverse correlation of the ratio YHC/CBDwith the volume of theright hippocampus was observed.
Conclusion: Lower volume in the right hippocampus in chronic cannabis users was corroborated. Higher THC and lower CBD were associated with this volume reduction indicating neurotoxic effects of THC and neuroprotctive effects of CBD, confirming previous preclinical and clinical results.

2010 Hanson et al found that marijuana users demonstrated poorer verbal learning, verbal working memory and attention memory compared to controls. Improvements were seen in users on word listlearning after 2 weeks of abstinence and on verbal working memory after 3 weeks. While attention processing speed was similar between groups, attention accuracy remained deficient throughout the 3 week abstinence period. These results implicate possible hippocampal, subcortical and prefrontal cortex abnormalities.

2010 Koskinen et al conducted a meta-analysis of the rate of cannabis use disorders (CUDs) in clinical samples of patients with schizophrenia. 35 studies were examined. The median current rate of CUDs was 16%(10 studies) and the median lifetime rate was 27.1% (28 studies). The median rate for CUDs was markedly higher in first episode vs long-term patients (current 28.6%/22.0%, lifetime 44.4%/12.2% respectively) and in studies where more than two thirds of the participants were male, than in the other studies (33.8%/13.2%). CUDs were also more common in younger samples than in the others (current 38.5%/16.0% lifetime 45.0%/17.9%). Conclusion: Approximately every 4th schizophrenia patient in our sample of studies had a diagnosis of CUDs. CUDs were especially common in younger and first-episode patient samples as well as in samples with a high proportion of males.

2011 Ali and others looked at the social contagion effect of marijuana use among adolescents. Their findings indicate that peer effects are important determinants of marijuana use even after controlling for potential biases. A 10% increase in the proportion of close friends and classmates that use cannabis increases the probability that an individual chooses to use marijuana by 5%.

2011 Buckner et al studied social anxiety and marijuana-related problems. The relationship between current (past 3 months) marijuana-related problems and 2 aspects of social anxiety (fear in social situations and social avoidance) among 102 current users was examined. Although both conditions were significantly correlated with marijuana-related problems, only social avoidance was uniquely related to marijuana problems after controlling for social fear, sex, negative effect, alcohol problems and marijuana use frequency. Sex moderated the relationship between social avoidance and marijuana related problems such that men with greater social avoidance exhibited the greatest severity of marijuana related problems. They conclude: Avoidance of social situations appears robustly related to marijuana-related problems.

2011 Feb, Solowij N and others studied verbal learning and memory in adolescent cannabis users, alcohol users and non-users aged 16 to 20. 181 adolescents took part. They found thatcannabis users performed significantly worse than alcohol users and non-users on all performance indices. The degree of impairment was associated with the duration, quantity, frequency and ageof onset of cannabis use, but unrelated to alcohol or any other drug use. The earlier the onset, the worse the memory performance.
Conclusions: Despite relatively brief exposure, adolescent cannabis users relative to their age-matched counterparts demonstrated similar memory deficits to those reported in adult long-term heavy uses. The results indicate that cannabis adversely affects the developing brain and reinforce concerns regarding the impact of early exposure.

2011 March Feinstein et al found that MS patients using marijuana to relieve pain were ‘hurting’ their thinking skills. The study used 25 patients and 25 controls. The users scored significantly lower on tests of attention, thinking speed and gauging space between objects. About 40 to 60% of people with MS have problems with decision making, thinking and reasoning. Pot smoking may be making this worse.

2011 June Fontes et al found that regular cannabis users, if they start before the age of 15 perform worse on brain tests than those who start leter. 104 chronic cannabis users, of whom 49 had started before the age of 15, took part in a series of tests involving, executive functionng, attention, perseverance, ability to form abstract concepts, visual and motor skills and mental flexibility. There was no difference between the groups or controls in terms of IQ. The early onset group performed significantly worse on attention, impulse control and executive functioning.

Dr Maria Fontes said, ‘We know that adolescence is a period in which the brain appears to be particularly vulnerable to the neurotoxic effects of cannabis’.

Gruber et al 2011 looked at age of onset of marijuana use and executive function. Age of onset, frequency, and magnitude of MJ use were all shown to impact cognitive performance. Findings suggest that earlier MJ onset is related to poorer cognitive function and increased frequency and magnitude of MJ use relative to later MJ onset. Exposure to MJ during a period of neurodevelopmental vulnerability, such as adolescence, may result in altered brain development and enduring neuropsychological changes.

2011 Crean and others conducted a review of executive functions and use of cannabis These are the conclusions: The trajectory of effects of cannabis on executive functions follows an interesting pattern of recovery of some functions and persisting deficits in others. The acute effects of cannabis use are evident in attentional and information processing abilities with recovery of these functions likely after a month or more of abstinence. Decision-making and risk-taking problems aren't necessarily evident immediately after smoking; however, if cannabis use is heavy and chronic, impairments may emerge that do not remit with abstinence, particularly if heavy use was initiated in adolescence such that maturation of executive functions was not achieved. Acute cannabis use impairs inhibition and promotes impulsivity, and over a period of abstinence, these deficits are most evident in tasks that require concept formation, planning and sequencing abilities. Working memory is significantly impaired following acute exposure to cannabis; however, these deficits resolve with sustained abstinence. Evidence is less clear in regards to verbal fluency abilities; however, research suggests that chronic, heavy use may impact verbal fluency abilities even after long-term abstinence. The long-term effects of cannabis on executive function is most clearly demonstrated when studies use chronic, heavy cannabis users, as opposed to light, occasional users. Yet even occasional cannabis use can acutely impair attention, concentration, decision-making, inhibition, impulsivity and working memory.

2012 Kucewicz looked at the fact that brain activity becomes uncoordinated and inaccurate during altered states of mind leading to neurophysiological and behavioural impairments reminiscent of schizophrenia. This study tested whether the detrimental effects of cannabis on memory and cognition could be the result of 'disorchesrated' brain networks. An agonist of THC was used on rats and completely disrupted co-ordinated brain waves across the hippocampus and prefrontal cortex. (like 2 sections of an orchestra playing out of sync. The rats became unable to make decisions while navigating round a maze.

2012 March Han et al found that acute cannabinoids can impair the working memory (the ability to retain and use information over short periods of time). A previously unknown signalling mechanism between neurons and non-neuronal cells called astrocytes (always thought to be merely supporting and protecting cells of neurons) has been found. 'Our study provides compelling evidence that astrocytes control neurons and memory, the supporting actor has become the leading actor' said Zhang, one of the authors. It was discovered that THC weakened the synapses between neurons in the hippocampus, crucial for memory formation, and this was controlled by the previously undiscovered CB1 receptors on the astrocytes.

2012 August, Zalesky et al (Australia) Looked at the effect of long-term cannabis use on axonal fibre connectivity. 59 people who had been using marijuana for 15 years on average were compared with scans (MRI) of 33 people who had never used the drug. The white matter in brains (complex wiring system) continues to develop over a lifetime. Changes to the volume, strength and integrity of the white matter were measured. Dr Seal, the lead researcher said there was a reduction in the volume of white matter of more than 80% of the users studied. The average age of initiation was 16 but there were some who had started at 10 or 11 – they were more seriously affected. Dr Seal said, 'This is the first study to demonstrate the age at which regular cannabis use begins is a key factor in determining the severity of the brain damage……We don't know if these changes are irreversible but we do know that these changes are quite significant……These people can have trouble learning new things and they are going to have trouble remembering things'.

2012 August, Meir et al as part of the long-running Dunedin Study, found that the IQ of children hooked on cannabis in their teens, and continuing to take it, fell by an average of 8 points (equivalent to dropping from average IQ to the lower third of the population). More than 1,000 children were out through a battery of tests at ages 13, 14 and then 38. None had tried cannabis when the research started making it easier to observe the effects of cannabis. Interviews on cannabis use were conducted at 18, 21,26, 32 and 38. Attention and memory were also harmed. Tests normally used to spot the early signs of Altzeimers were conducted and adolescent cannabis users fared worse. The effects on IQ could still be seen in those who had not touched cannabis for a year. Small falls in IQs were seen in those who never or occasionally used the drug and those who had started to use it as an adult.

2013 Jan Rogeberg (edited by Iverson) challenged the Meir paper above:

Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status

Abstract

Does cannabis use have substantial and permanent effects on neuropsychological functioning? Renewed and intense attention to the issue has followed recent research on the Dunedin cohort, which found a positive association between, on the one hand, adolescent-onset cannabis use and dependence and, on the other hand, a decline in IQ from childhood to adulthood [Meier et al. (2012) *Proc Natl Acad Sci USA* 109(40):E2657–E2664]. The association is given a causal interpretation by the authors, but existing research suggests an alternative confounding model based on time-varying effects of socioeconomic status on IQ. A simulation of the confounding model reproduces the reported associations from the Dunedin cohort, suggesting that the causal effects estimated in Meier et al. are likely to be overestimates, and that the true effect could be zero. Further analyses of the Dunedin cohort are proposed to distinguish between the competing interpretations. Although it would be too strong to say that the results have been discredited, the methodology is flawed and the causal inference drawn from the results premature.

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Specifically, the new study (Rogeberg) uses simulation models to suggest that other factors, such as socioeconomic status, may account for the downward IQ trend seen in the Meier et al. study. Indeed, when discussing traits like IQ, it would be surprising for one factor to be 100 percent causal. The strengths of the Meier et al study are that it is longitudinal in nature and that it controlled for a number of factors including years of education, schizophrenia, and other substance abuse. That said, observational studies in humans cannot account for all potentially confounding variables. In contrast, animal studies—though limited in their application to the complex human brain—can more definitively assess the relationship between drug exposure and various outcomes. They have shown that exposure to cannabinoids during adolescent development can cause long-lasting changes in the brain's reward system as well as the hippocampus, a brain area critical for learning and memory.
The message inherent in these and in multiple supporting studies is clear. Regular marijuana use in adolescence is known to be part of a cluster of behaviors that can produce enduring detrimental effects and alter the trajectory of a young person's life—thwarting his or her potential. Beyond potentially lowering IQ, teen marijuana use is linked to school dropout, other drug use, mental health problems, etc. Given the current number of regular marijuana users (about 1 in 15 high school seniors) and the possibility of this number increasing with marijuana legalization, we cannot afford to divert our focus from the central point: regular marijuana use stands to jeopardize a young person's chances of success—in school and in life.

Madeline Meier, a psychologist at the Duke Transdisciplinary Prevention Research Center in Durham, North Carolina, who co-wrote the original paper with her colleagues, says that Røgeberg's ideas are interesting. However, she points out that the authors of the first *PNAS* paper restricted their analysis to individuals in middle-class families and those with low or high socioeconomic status. The outcome suggests that the decline in IQ cannot be attributed to socioeconomic factors alone.

In their original analysis, Meier says, she and her colleagues controlled for socioeconomic status and found that in all socioeconomic categories, the IQs of children who were not heavy users remained unchanged from adolescence to adulthood. Therefore, she says, socioeconomic status does not influence IQ decline.

Science experts defend the Meier paper:

http://www.sciencemediacentre.co.nz/2012/08/28/teen-cannabis-use-and-iq-experts-respond/

2012 September Long et al, ' The system of the brain responsible for mediating effects of cannabis, the endo-cannabinoid system, is most vulnerable to the drug during adolescence' .Dr Leonora Long said, ' During adolescence the endo-cannabinoid system in the brain undergoes a lot of change, and interfering with these changes by using cannabis could have consequences for the development of healthy brains in adults. Cannabis use is common among teens and adolescents, and adolescence is a time when adult behaviours and decision-making are developing. so this discovery is very significant.
The endocannabinoid system is involved in appetite, pain sensation, mood and memory, and affects the way neurons in the brain communicate with each other.

2013 Blakemore SJ looked at cannabis and the adolescent brain. She supported the research by Meir in August 2012 about IQ resulting from The Dunedin Study.

2013 Raver and others found that adolescent cannabinoid exposure permanently suppresses cortical oscillations in adult mice, thus permanently altering working-memory performance in adults. 'To our knowledge, ours is the first study to demonstrate a direct link between cannabinoid exposure specifically during adolescence and abnormal electrophysiological activity in the adult neocortex, as well as to report a differential vulnerability of cortical regions that parallels their maturational state at the time of drug exposure'.

2013 Bloomfield et al compared dopamine synthesis capacity in 19 regular cannabis users who experienced psychotic-like symptoms when they consumed cannabis with 19 non-user, sex and age matched control subjects. The results surprised them. Cannabis users had reduced dopamine synthesis capacity in the striatum and its associative and limbic sub-divisions compared with the controls. These results were seen in those users meeting abuse or dependence criteria. Dopamine synthesis capacity was negatively associated with higher levels of cannabis use and positively associated with age of onset of use, but not with cannabis induced psychotic-like symptoms. They concluded, ' these findings indicate that chronic cannabis use is associated with reduced dopamine synthesis capacity and question the hypothesis that cannabis increases the risk of psychotic disorders by inducing the same dopaminergic alterations seen in schizophrenia.

2013 Dominquez and others examined the duration of untreated psychosis in adolescents: ethnic differences and clinical profiles. 940 new first-episode psychosis cases aged 14-35 (136 adolescent onset versus 804 adult onset individuals). Age of onset, family mental heath history, duration of untreated psychosis (DUP), suicidality and substance use info, were all collected at entry. Adolescents had significantly greater median DUP (179 days) than adults (81 days).Among adolescent ethnic groups, Median DUP whites – 454 days (DOH Target =3 months), black - 103 days, Asian and mixed - 28.5 days. Younger onset and higher lifetime cannabis users were associated with longer treatment delay.

2013 Mechoulam and Parker looked at CBD effects. They found CBD opposes some but not all forms of behavioural and memory disruption caused by THC in male Rhesus monkeys.

Professor Sir Robin Murray commented:

'Acute TCH increases striatal dopamine but we have known for some time that chronic dependence on drugs such as amphetamine or alcohol seems to depress striatal dopamine levels. Because dopamine is involved in reward this drives them to take more drugs to try and increase their dopamine back to normal. So this paper shows that cannabis acts like other drugs of abuse in that if you keep taking it your dopamine levels become low.

Recently it was reported by Dr Anissa Abi-Dharghum cannabis dependent people with psychosis symptoms also had low striatal dopamine but if they were given amphetamine they developed exacerbation of their psychosis even with a tiny increase in striatal dopamine (within normal limits). So it may be that the cannabis users who develop psychosis may have somehow developed a supersensitive dopamine system. This could be because of an abnormality further downstream. For example, you know that we have shown an effect of the gene AKT1. This has a role in post-receptor signalling i.e. after the dopamine receptor. So, it is possible that a person with the AKT1 risk variant might have so sensitive a dopamine system that psychotic symptoms might ensue even with a small change in striatal dopamine.

So the above remains a possibility. An alternative is that an effect on the CB1 receptor directly affects AKT without going through the Dopamine system.

Another alternative is something entirely different that we can't even speculate about. So the bottom line is that we don't have a definitive answer. But at least people are now seriously looking at these questions'.

2014 Homel et al looked at associations between longitudinal trajectories of marijuana use from adolescence to young adulthood (15-25) and PSE (Post Secondary Education) experiences. They concluded that 'Frequent marijuana use from adolescence to young adulthood may close off opportunities for entering PSE. Occasional users may create delays in starting and finishing PSE among less-at-risk young people'.

2014 Silins et al investigated adolescent use and the consequences for young adults using 3 large long-running studies involving 3765 individuals in Australia and New Zealand (Australian Temperament Project, the Christchurch Health and Development Study and the Victorian Adolescent Health Cohort). Findings included: teenagers using cannabis daily before age 17 were 60% less likely to complete high school/university compared with never-users. They were also 7 times more likely to attempt suicide and 8 times as likely to use other illicit drugs. The authors linked frequency of use with 7 developmental outcomes to the age of 30: completing high school, obtaining a university degree, cannabis dependence, use

of other illicit drugs, suicide attempts, depression and welfare dependence. A clear association was found wit frequency of use in adolescence and poor outcomes across most measures, even after controlling for socio-economic status, mental illness etc. Risk increased as amount taken rose.

2014 Mokrysz et al looked at educational and intellectual performance of 2612 children between the ages of 8 and 15, the IQs of these children were noted at these ages. Cannabis use was investigated for its role in educational performance. They found no relationship between canabis use and lower IQ at age 15. Heavier cannabis users (at least 50 times by age 15) did show marginally impaired educational abilities (exam results 3% lower).

The study was criticised: cannabis use was self-reportedand the measure of IQ at age 15 was an abbreviated versaion of the standard Wechsler IQ test.

Dr Madeline Meir (Dunedin Study) says,

"This new paper looks interesting. It does not relate in any way to our findings from The Dunedin Study, however.

Our finding was that adults who were long-term dependent on cannabis and those who used cannabis 4 or more times/week during the 20 years after adolescence, had lost 8 IQ points by age 38.

Those who has lost the most IQ points were those who had started their cannabis use youngest, as teens.

There is no reason to expect that teens who have used cannabis only 50 times would already show a loss of IQ points by age 15.

The ALSPAC (Avon Longitudinal Study of Parents and Children) would need at least 20 more years of follow up, and data on cannabis dependence, before it could be compared to the Dunedin Study"

2014 Conroy et al looked at the impact of marijuana use on self-rated cognition in young adult men and women. Forty eight young adults participated (22 female) mean age 22.3 years. There was a significant relationship between greater number of minutes of marijuana use and higher levels of self-related cognitive difficulties. Gender was not significant.

2014 Ehrenreich et al looked at marijuana use from Middle to High School and co-occurring problem behaviours, teacher –related academic skills and sixth grade predictions. 619 randomly selected students were assessed annually from 6th to 12th grade. They were grouped : Abstainer (65.6 %), Sporadic (13.9 %), Experimental (11.5 %), and Increasing (9.0 %). Compared to Abstainers, students in the Sporadic, Experimental and Increasing trajectories reported significantly more co-occurring problem behaviors of alcohol use, cigarette smoking, and physical aggression. Sporadic and Experimental users reported significantly less smoking and physical aggression, but not alcohol use, than Increasing users. Teachers consistently rated Abstainers as having better study skills and less attention and learning problems than the three marijuana use groups. Compared to Abstainers, the odds of dropping out of high school was at least 2.7 times higher for students in the marijuana use trajectories. Dropout rates did not vary significantly between marijuana use groups. In sixth grade, being male, cigarette smoking, physical aggression and attention problems increased the odds of being in the marijuana use trajectories. Multiple indicators-student self-reports, teacher ratings and high school dropout records-showed that marijuana was not an isolated or benign event in the life of adolescents but part of an overall problem behavior syndrome.

Stiby et al looked at the educational outcomes of adolescent cannabis and tobacco smokers at age 16. The sample was drawn from The Avon Longitudinal Study of parents and Children (1,155 individuals). GCSE results in English and Mathematics were investigated. Both weekly cannabis use and daily tobacco use were associated at age 15 with subsequent adverse educational outcomes.

2015 Smith et al discovered that teens who were heavy marijuana smokers (16-17 year olds at start daily for around 3 years) had an abnormally-shaped hippocampus and performed poorly on long-term memory tasks. The hippocampus is important to long-term memory (remembering life events). The brain abnormalities were observed during the individuals' early twenties, two years after they had stopped smoking marijuana. Young adults who abused cannabis as teenagers performed about 18% worse on long-term memory tests than those who had never abused cannabis. There were 97 participants who used no other drugs. The study also found that young adults with schizophrenia who abused cannabis as teens,

performed about 26% more poorly on memory tests than young adults with schizophrenia who had never abused cannabis.

2015 Dudok and others carried out cell-specific super-resolution imaging to reveal nanoscale organisation of cannabinoid signalling. They found that recreational smoking of cannabis can dramatically reduce the number of molecules ensuring the fine-tuning of brain functions and significantly interferes in the two-way communication between neurons.Research showed that the number of receptors in synapses receiving endocannabinoid molecules decreased dramatically by around 85% after a six-day THC treatment, with total regeneration taking as long as six weeks. Hese findings indicate that cell type-specific nano-scale analysis of endogenous protein distribution is possible in brain circuits and identify previously unknown molecular properties controlling endocannabinoid signalling and cannabis-induced cognitive dysfunction.

2015 April Riba et al found that cannabis consumers show greater susceptibility to false memories. Chronic consumers show more difficulties than the general population in retaining new information and recovering memories. Chronic use also causes distortions in memory, making it easier for imaginery or false memories to appear. On occasion the brain can remember things that never happened. This can occur even weeks after consumption has stopped.

2015 Jacobus et al studied Neuropsychological performance in adolescent marijuana users with co-occuring alcohol use over 3 years. Adolescent marijuana users with concomitant alcohol use (MJ + ALC, n = 49) and control teens with limited substance use histories (CON, n = 59) were given neuropsychological and substance use assessments at project baseline, when they were ages 16-19. They were then reassessed 18 and 36 months later. MJ + ALC users performed significantly worse than controls, across time points, in the domains of complex attention, memory, processing speed, and visuospatial functioning. Earlier age of marijuana use onset was associated with poorer processing speed and executive functioning by the 3-year follow-up. They concluded that frequent marijuana use throughout adolescence and into young adulthood appeared linked to worsened cognitive performance. Earlier age of onset appears to be associated with poorer neurocognitive outcomes that emerge by young adulthood, providing further support for the notion that the brain may be uniquely sensitive to frequent marijuana exposure during the adolescent phase of neurodevelopment.

2015 Olivier and Ulf investigated cannabis access and academic performance. Discrimination against legality was introduced on terms of nationality. 54,000 course grades of students in Maastricht were examined before and after ‘legal’ cannabis. The academic performance of students no longer legally permitted to buy cannabis increased substantially. Effects were stronger for women and low performers.

2015 Becker et al found longitudinal changes in white matter microstructure after heavy cannabis use. 23 young adults(18-20 years), regular users were paired with 23 age, sex and IQ matched non-using controls. Onset of cannabis use was before 17.Reduced longitudinal growth in several areas of the brain. Greater amounts of cannabis use correlated with greater longitudinal reduction, as was relatively impaired performance on a measure of verbal learning. Heavy cannabis use in adolescence and early adulthoodalters ongoing development of white matter microstructure, contributing to functional impairment.

2015 Arria et al used a large longitudinal cohort study of college students to test the direct and indirect effects of marijuana use on college grade point average (GPA) and time to graduate, with skipping classes as a mediator of these outcomes. The results showed a significant path from baseline marijuana use frequently to skipping classes at baseline to lower first semester GPA to longer time to graduate. Over time the rate of change in marijuana use was negatively associated with rate of change of GPA, but did not account for any additional variance in graduation time. Percentage of classes skipped was negatively associated with GPA at baseline and over time.

2015 Rigucci et al investigated the effect of high-potency cannabis on the microstructure of the corpus callosum (crucial part of brain responsible for communication between the two brain hemispheres, composed of white matter fibres, called axons). They found ‘the more cannabis you smoke and the higher the potency the worse the damage will be’. They examined the white matter in the brains of 56 people who reported a first episode psychosis at the South London and Maudsley NHS Foundation Trust, and 43 healthy participants from the local area. They also discovered that ‘frequent use of high potency cannabis significantly affects the structure of white matter fibres in the brain whether you have psychosis or not’. The worst damage (lesions) was seen in the most posterior part of the corpus callosum.

2016 Auer et al looked at the association between lifetime marijuana use and cognitive function in middle age. 5115 black and white men and women between 18 and 30 were followed up over 25 years. After

excluding current users and adjusting for potential confounders, cumulative lifetime exposure to marijuana remained significantly associated with worse verbal memory.

2016 Nunez et al investigated heavy cannabis use and cognitive function in first episode psychosis. They found that haeavy cannabis consumption seems to impair verbal memory in first psychotic episode patients Heavy users also peformed worse than medium users in other neurocognitive tests. Non-users performed better than all cannabis users in the arithmetic test.

2016 Suerken et al investigated the academic outcomes among college students. 'Five marijuana trajectory groups were identified: non-users (69.0%), infrequent users (16.6%), decreasing users (4.7%), increasing users (5.8%), and frequent users (3.9%). Decreasing users and frequent users were more likely to drop out of college and plan to delay graduation when compared to non-users. All marijuana user groups reported lower GPA (Grade Point Averages), on average, than non-users.

These results identify marijuana use patterns that put students at risk for poor academic performance in college. Students who use marijuana frequently at the beginning of the college career are especially at risk for lower academic achievement than non-users.

2016 Dahlgren et al examined whether marijuana use could predict the cognitive performance of executive function. They included earlier age at onset, higher frequency, and increased magnitude of use. They found that marijuana smokers had poorer executive function relative to control participants, a between-group difference that was primarily driven by individuals with early onset of marijuana use (before age 16; n = 21); significance remained even when controlling for frequency and magnitude of use. Further, earlier age at marijuana onset and increased marijuana use predicted poorer neurocognitive performance, and perseverative errors on the WCST (Wisconsin Card Sorting Test) significantly predicted marijuana group membership.

2016 D'Amico et al looked at adolescent alcohol and marijuana use in connection with academic and health problems. A total of 6509 adolescents completed 7 surveys between 2008 and 2015. Those who use both alcohol and marijuana during middle and high school are more likely to have poorer academic performance and mental health. They also had poorer academic functioning, being less prepared for school and have more delinquent behaviour. Non-white youth tend to experience poorer functioning than white youth. Confounding factors may be racial discrimination, parental involvement or neighbourhood quality.

2016 Silveira et al investigated 'laziness' in cannabis users. They tested the hypothesis that THC impairs a relevant cognitive function for long-term success, namely willingness to exert cognitive effort for greater rewards, and that CBD could attenuate such decision-making impairments.
29 male Long–Evans rats performing the rat cognitive effort task (rCET) received acute THC and CBD, independently and concurrently, in addition to other cannabinoids. Rats chose between 2 options differing in reward magnitude, but also in the cognitive effort (attentional load) required to obtain them. They found that THC decreased choice of hard trials without impairing the animals' ability to accurately complete them. In contrast, CBD did not affect choice. Co-administration of 1:1 CBD:THC modestly attenuated the deleterious effects of THC in "slacker" rats. Only male rats were investigated, and the THC/CBD co-administration experiment was carried out in a subset of individuals. They concluded that: These findings confirm that THC, but not CBD, selectively impairs decision-making involving cognitive effort costs. However, co-administration of CBD only partially ameliorates such THC-induced dysfunction.

2016 Plunk et al looked at medical cannabis legalization and school drop-out rates. Data from the 2000 Census and 2001–2014 American Community Surveys were restricted to individuals who were of high school age (14–18) between 1990 and 2012 (n = 5,483,715). 'Medical Marijuana Laws (MML) were associated with a 0.40 percentage point increase in the probability of not earning a high school diploma after completing the 12th grade (from 3.99% to 4.39%). High school MML exposure was also associated with a 1.84 and 0.85 percentage point increase in the probability of college non-enrollment and degree non-completion, (from 31.12% to 32.96% and 45.30% to 46.15%, respectively). Years of MML exposure exhibited a consistent dose response relationship for all outcomes. MMLs were also associated with 0.85 percentage point increase in daily marijuana use among 12th graders (up from 1.26%)'. They concluded that 'Medical marijuana law exposure between age 14 to 18 likely has a delayed effect on use and education that persists over time'.

2016 Hebert-Chatelain et al looked at memory loss and cannabis and its relationship to mitochondrial harm. Mitochondria are small organelles in most cells responsible for energy regulation. Research has shown that cannabis can cause memory loss. The researchers found that chemicals in cannabis attach to CB1 receptors in mitochondria in brain cells in the hippocampus where memory processing occurs. It is suggested that

memory loss may be due to cannabis use and its impact on these organelles. They suggest their findings indicatethat chronic use of the drug could cause permanent damage to mitochondria leading to long-term or permanent memory loss.

2016 Powell-Booth et al looked at the impact of cannabis on the neuro-cognitive performance of Jamaican adolescents. The sample consisted of 62 male students – 30 cannabis users and 32 non-users, between 13 and 17 years of age. There was a significant difference between the performance of cannabis users and non-users on all tests of learning, memory and attention.

2017 Meda et al Looked at the longitudinal influence of alcohol and marijuana use on academic performance in college students. The longitudinal 2-year Brain and Alcohol Research in College Students provided the data. 1142 freshman students completed monthly alcohol and marijuana surveys. 3 clusters emerged 1. No/low users of both, 2. medium-high alcohol /no marijuana and 3. medium- high users of both. Group 2 demonsrate low GPAs (Grade Point Average) compared to non-users, but the difference becomes non significant over time. Group 3 students score lower at outset and this continues over the 2-year time scale.

2017 Williams et al looked at academic ability in children in relation to cigarette, alcohol and cannabis use. Data from 7 years of the longitudinal Study of Young People in England, 2004 - 2010 was used. Ages were 13/14 to 19/20. 6059 (3093 females) provided information about academic ability and health at age 11. High v low academic ability reduced the risk of persistent cigarette smoking in early adolescence. High v low ability increased the risk of occasional and persistent regular alcohol drinking in early adolescence and persistent but not occasional regular alcohol drinking in late adolescence. High academic ability was also positively associated with occasional and persistent cannabis use in late adolescence. They concluded that: High childhood academic ability at age 11 is associated with reduced risk of cigarette smoking but increased risk of drinking alcohol regularly and cannabis use. These associations persist into adulthood providing evidence against the hypothesis that high academic ability is associated with temporary 'experimentation' with substance use.

2017 Filbey et al investigated the age of starting use of marijuana and whether it had long-term effects on brain development. 'Although groups (early onset >16 and later onset >16) did not differ by onset status, groups diverged in their correlations between cannabis use and cortical architecture. Among early-onset users, continued years of MJ use and current MJ consumption were associated with thicker cortex, increased GWR (gray/white matter border contrast) and decreased LGI(Local Gyrification Index) Late-onset users exhibited the opposite pattern. This divergence was observed in all three morphological measures in the anterior dorso-lateral frontal cortex'. 'Divergent patterns between current MJ use and elements of cortical architecture were associated with early MJ use onset. Considering brain development in early adolescence, findings are consistent with disruptions in pruning. However, divergence with continued use for many years thereafter suggests altered trajectories of brain maturation during late adolescence and beyond'.

2017 Patte et al looked at marijuana and alcohol use as predictors of academic achievement. 26,475 grade 9-12 student with at least 2 years of linked longitudinal data were tested for the likelihood of responses to measures of academic goals, engagement, preparedness, and performance when shifting from never using alcohol or marijuana at baseline to using them at varying frequencies at follow -up. 'Students who began using alcohol or marijuana were less likely to attend class regularly, complete their homework, achieve high marks, and value good grades, relative to their abstaining peers. Changing from abstaining to rare/sporadic-to-weekly drinking or rare/sporadic marijuana use predicted aspirations to continue to all levels of higher education, and initiating weekly marijuana use increased the likelihood of college ambitions, while more regular marijuana use reduced the likelihood of wanting to pursue graduate/professional degrees, over high school.

2017 Melchior et al studied early cannabis initiation and educational attainment. 'Analyses are based on data collected among TEMPO cohort study participants (France, 2009, n = 1103, 22-35 years). Participants were previously assessed in childhood (1991) and adolescence (1999); additionally, their parents had taken part in a longitudinal epidemiological cohort study (GAZEL). Early cannabis initiation was defined as use at age 16 or earlier. Educational attainment was defined as the completion of a high-school degree ('Baccalauréat'). Early (up to and including age 16 years) and late (after age 16 years) cannabis-use initiators were compared with non-users. In age- and sex-adjusted analyses, early cannabis initiators were more likely than non-users to have low educational attainment [odds ratio (OR): 1.77. Late cannabis

initiators did not have lower educational attainment than non-users. Early cannabis use and educational attainment appeared more strongly associated in young women than in young men.

2017 Castellanos-Ryan et al looked at adolescent cannabis use and neurocognitive performance. 'The main objective of this prospective longitudinal study was to investigate bidirectional associations between adolescent cannabis use (CU) and neurocognitive performance in a community sample of 294 young men from ages 13 to 20 years. The results showed that in early adolescence, and prior to initiation to CU, poor short-term and working memory, but high verbal IQ, were associated with earlier age of onset of CU. In turn, age of CU onset and CU frequency across adolescence were associated with (a) specific neurocognitive decline in verbal IQ and executive function tasks tapping trial and error learning and reward processing by early adulthood and (b) lower rates of high-school graduation. The association between CU onset and change in neurocognitive function, however, was found to be accounted for by CU frequency. Whereas the link between CU frequency across adolescence and change in verbal IQ was explained (mediated) by high school graduation, the link between CU frequency and tasks tapping trial and error learning were independent from high school graduation, concurrent cannabis and other substance use, adolescent alcohol use, and externalizing behaviors. Findings support prevention efforts aimed at delaying onset and reducing frequency of CU'.

2017 Meier et al looked at the association between adolescent cannabis use and neuropsychological decline in a longitudinal co-twin control study. Abstract: Participants were 1989 twins from the Environmental Risk (E-Risk) Longitudinal Twin Study, a nationally representative birth cohort of twins born in England and Wales from 1994 to 1995. Frequency of cannabis use and cannabis dependence were assessed at age 18. Intelligence quotient (IQ) was obtained at ages 5, 12 and 18. Executive functions were assessed at age 18. Compared with adolescents who did not use cannabis, adolescents who used cannabis had lower IQ in childhood prior to cannabis initiation and lower IQ at age 18, but there was little evidence that cannabis use was associated with IQ decline from ages 12-18. For example, adolescents with cannabis dependence had age 12 and age 18 IQ scores that were 5.61 ($t = -3.11$, $P = 0.002$) and 7.34 IQ points ($t = -5.27$, $P < 0.001$) lower than adolescents without cannabis dependence, but adolescents with cannabis dependence did not show greater IQ decline from age 12-18 ($t = -1.27$, $P = 0.20$). Moreover, adolescents who used cannabis had poorer executive functions at age 18 than adolescents who did not use cannabis, but these associations were generally not apparent within twin pairs. For example, twins who used cannabis more frequently than their co-twin performed similarly to their co-twin on five of six executive function tests ($Ps > 0.10$). The one exception was that twins who used cannabis more frequently than their co-twin performed worse on one working memory test (Spatial Span reversed; $\beta = -0.07$, $P = 0.036$). Short-term cannabis use in adolescence does not appear to cause IQ decline or impair executive functions, even when cannabis use reaches the level of dependence. Family background factors explain why adolescent cannabis users perform worse on IQ and executive function tests.

2018 Mouro et al investigated the harm done to the brain by cannabis and cannabis-based drugs. A new study led by Ana Sebastião, group leader at Instituto de Medicina Molecular João Lobo Antunes and Professor of Faculdade de Medicina of Universidade de Lisboa (iMM, FMUL; Portugal) and her team in collaboration with researchers from the University of Lancaster (UK), shows that the long-term use of either cannabis or cannabis-based drugs impairs memory. The study now published in the *Journal of Neurochemistry* reveals the implications for both recreational users and people who use the drug to combat epilepsy, multiple sclerosis and chronic pain. Through the legalisation in several countries of cannabis or cannabis-based drugs, there is an increased number of long-term users and more potent varieties are available for recreational users. It is already known that heavy, regular cannabis use increases the risk of developing mental health problems including psychosis and schizophrenia. However, there is still little understanding of the potential negative side effects of long-term cannabinoid exposure. Now, the research group led by Ana Sebastião in collaboration with Neil Dawson and his team at Lancaster University studied the effects of a specific cannabinoid drug (named WIN 55,212-2) and found that mice exposed for long-term to the drug had "significant memory impairments" and could not even discriminate between a familiar and novel object. Also, brain imaging studies showed that the drug impairs function in key brain regions involved in learning and memory. Moreover, the long-term exposure to the drug impairs the ability of brain regions involved in learning and memory to communicate with each other, suggesting that this underlies the negative effects of the drug on memory. "Importantly, our work clearly shows that prolonged cannabinoid intake, when not used for medical reasons, does have a negative impact in brain function and memory. It is important to understand that the same medicine may re-establish an equilibrium under certain diseased conditions, such as in epilepsy or multiple sclerosis, but could cause marked imbalances in healthy individuals. As for all medicines, cannabinoid-based therapies have not only beneficial disease-related actions, but also negative side effects", says Ana Sebastião. A previous study from the same team has showed that acute exposure to cannabinoids results in recognition memory deficits, an effect that can be

prevented by the use of a drug of the family of caffeine. "These results are very important for the development of pharmacological strategies aiming to decrease cognitive side effects of currently used cannabinoid-based therapies, which proved effective against several nervous system disorders", explains Ana Sebastião. "This work offers valuable new insight into the way in which long-term cannabinoid exposure negatively impacts on the brain. Understanding these mechanisms is central to understanding how long-term cannabinoid exposure increases the risk of developing mental health issues and memory problems; only its understanding will allow to mitigate them", says Neil Dawson.

2018 Morin et al conducted a population-based analysis of the relationship between substance use and adolescent cognitive development. Abstract: Alcohol and cannabis misuse are related to impaired cognition. When inferring causality, four nonexclusive theoretical models can account for this association: 1) a common underlying vulnerability model; 2) a neuroplasticity model in which impairment is concurrent with changes in substance use but temporary because of neuroplastic brain processes that restore function; 3) a neurotoxicity model of long-term impairment consequential to substance use; and 4) a developmental sensitivity hypothesis of age-specific effects. Using a developmentally sensitive design, the authors investigated relationships between year-to-year changes in substance use and cognitive development. A population-based sample of 3,826 seventh-grade students from 31 schools consisting of 5% of all students entering high school in 2012 and 2013 in the Greater Montreal region were assessed annually for 4 years on alcohol and cannabis use, recall memory, perceptual reasoning, inhibition, and working memory, using school-based computerized assessments. Multilevel regression models, performed separately for each substance, were used to simultaneously test vulnerability (between-subject) and concurrent and lagged within-subject effects on each cognitive domain.Common vulnerability effects were detected for cannabis and alcohol on all domains. Cannabis use, but not alcohol consumption, showed lagged (neurotoxic) effects on inhibitory control and working memory and concurrent effects on delayed memory recall and perceptual reasoning (with some evidence of developmental sensitivity). Cannabis effects were independent of any alcohol effects.Beyond the role of cognition in vulnerability to substance use, the concurrent and lasting effects of adolescent cannabis use can be observed on important cognitive functions and appear to be more pronounced than those observed for alcohol.

2018 Schuster et al looked at abstinence from cannabis for a month and memory. Eighty-eight adolescents and young adults (aged 16–25 years) who used cannabis regularly were recruited from the community and a local high school between July 2015 and December 2016. Participants were randomly assigned to 4 weeks of cannabis abstinence, verified by decreasing 11-nor-9-carboxy-Δ9-tetrahydrocannabinol urine concentration (MJ-Abst; n = 62), or a monitoring control condition with no abstinence requirement (MJ-Mon; n = 26). Attention and memory were assessed at baseline and weekly for 4 weeks with the Cambridge Neuropsychological Test Automated Battery. ***:*** Among MJ-Abst participants, 55 (88.7%) met a priori criteria for biochemically confirmed 30-day continuous abstinence. There was an effect of abstinence on verbal memory (P = .002) that was consistent across 4 weeks of abstinence, with no time-by-abstinence interaction, and was driven by improved verbal learning in the first week of abstinence. MJ-Abst participants had better memory overall and at weeks 1, 2, 3 than MJ-Mon participants, and only MJ-Abst participants improved in memory from baseline to week 1. There was no effect of abstinence on attention: both groups improved similarly, consistent with a practice effect. This study suggests that cannabis abstinence is associated with improvements in verbal learning that appear to occur largely in the first week following last use. Future studies are needed to determine whether the improvement in cognition with abstinence is associated with improvement in academic and other functional outcomes.

2018 Miller et al found that THC exposure affects brain maturation in adolescent animals. This study Showed that rats will forgo heroin and methamphetamine in favor of spending time with another rat. Highlights the importance of incorporating voluntary choice between drugs and social rewards in drug addiction research and introduces a novel model for studying the impact of social motivation in studies of drug use and addiction

2019 Orr et al looked at grey matter volume differences associated with extremely low levels of cannabis use in adolescence. Abstract:Rates of cannabis use among adolescents are high, and are increasing concurrent with changes in the legal status of marijuana and societal attitudes regarding its use. Recreational cannabis use is understudied, especially in the adolescent period when neural maturation may make users particularly vulnerable to the effects of Δ-9-tetrahydrocannabinol (THC) on brain structure. In the current study, we used voxel-based morphometry to compare grey matter volume (GMV) in 46 fourteen year old human adolescents (males and females) with just one or two instances of cannabis use and

carefully matched THC-naïve controls. We identified extensive regions in the bilateral medial temporal lobes as well as the bilateral posterior cingulate, lingual gyri, and cerebellum that showed greater GMV in the cannabis users. Analysis of longitudinal data confirmed that GMV differences were unlikely to precede cannabis use. GMV in the temporal regions was associated with contemporaneous performance on the Perceptual Reasoning Index and with future generalized anxiety symptoms in the cannabis users. The distribution of GMV effects mapped onto biomarkers of the endogenous cannabinoid system providing insight into possible mechanisms for these effects. Almost 35% of American 10th graders have reported using cannabis and existing research suggests that initiation of cannabis use in adolescence is associated with long-term neurocognitive effects. We understand very little about the earliest effects of cannabis use, however, as most research is conducted in adults with a heavy pattern of lifetime use. This study presents evidence suggesting structural brain and cognitive effects of just one or two instances of cannabis use in adolescence. Converging evidence suggests a role for the endocannabinoid system in these effects. This research is particularly timely as the legal status of cannabis is changing in many jurisdictions and the perceived risk by youth associated with smoking cannabis has declined in recent years.

2019 Conrad et al looked at the neurobiological consequendes of adolescent cannabis use. Dr. Patricia Conrod, at Université de Montréal, studied the year-to-year changes in alcohol and cannabis use and cognitive function in a sample of adolescents consisting of 5% of all students entering high school in 2012 and 2013 in the Greater Montreal region (a total of 3,826 7th grade students). Students were assessed annually for 4 years on alcohol and cannabis use, and their cognitive function was evaluated using computarized cognitive tests. The researchers found substance use to be linked to low cognitive functioning, a finding that could be indicative of an underlying common vulnerability. Cannabis use was linked to impairments in working memory and inhibitory control, which is required for self-control. Cannabis use was also linked to deficits in memory recall and perceptual reasoning. Alcohol use was not linked to impairments in these cognitive functions, suggesting cannabis could have more long-term effects than alcohol.2019 Pelker et al found that recent cannabis use was tied to memory deficits and slowed mental processing. Participants were 1121 adults (54% female) enrolled in the Human Connectome Project. Cannabis involvement comprised recent cannabis use (positive tetrahydrocannabinol screen), total number of lifetime uses, cannabis use disorder and age at first use. The neuropsychological battery comprised performance in episodic memory, fluid intelligence, attention, working memory, executive function, impulsive decision-making, processing speed and psychomotor dexterity. Covariates were age, sex, income, family structure and alcohol and tobacco use. RESULTS: Positive urinary tetrahydrocannabinol status was associated with worse performance in episodic memory and processing speed, and positive cannabis use disorder status was associated with lower fluid intelligence (all $p < 0.005$). No other significant associations were present. LIMITATIONS:The sample was limited to young adults aged 22–36 years. The measures of cannabis involvement were relatively coarse.CONCLUSION:Beyond an array of potential confounders, recent cannabis use was associated with deficits in memory and psychomotor performance, and cannabis use disorder was associated with lower overall cognitive functioning in a large normative sample of adults. The findings pertaining to recent use have particular relevance for occupational settings.

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2020 Kloft et al looked at cannabis and the increase of false memory. Significance:
This unique randomized, double-blind, placebo-controlled trial examined the susceptibility to false memories under the influence of cannabis, using a basic (DRM) and two applied (misinformation) paradigms. We used a highly powered experimental design, allowing us to test acute and residual drug effects. To achieve high reproducibility and ecological validity, the misinformation paradigms included an eyewitness and a perpetrator scenario, presented in a virtual-reality

environment. We show across different paradigms that cannabis consistently increases susceptibility to false memories. The results have implications for police, legal professionals, and policymakers with regard to the treatment of cannabis-intoxicated witnesses and suspects and the validity of their statements.

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Cannabis and Mental Illness (Psychosis/schizophrenia) and Brain Damage

Cannabis – some very old papers:

Let's take a look at what physicians from a time untainted by politics, drug morality, or profit motive had to say about cannabis risks:

"In large doses it will produce hallucinations, which, in some, are of merriment and in others of a violent nature, even tendency to crime… Its habitual use will cause insanity"

Materia Medica and Clinical Therapeutics, by Fred Petersen, published in 1905
The most common effect, however, is the development of insanities which have been known for many years… Chronic mania and dementia represent terminal stages"

A Textbook of Materia Medica, Pharmacology and Therapeutics, by George F. Butler, published in 1908
"Repeated use of the drug produces mental weakness and [mental] impotence, the result of over-stimulation."

A Compend of Materia Medica, Therapeutics, Prescription Writing: With Especial Reference to the Physiological Actions of Drugs, by Samuel O.L. Potter, published in 1890
"Sometimes the delirium induced by hemp causes the individual to do deeds of violence, but does not act upon all alike… The after-effects are those of depression."

Materia Medica and Therapeutics for Physicians and Students, by John Biddle, published in 1895
"Hallucinations occur, but they are not usually agreeable; they are often painful and are replaced by stupor… Not unfrequently the excitement takes the form of a furious delirium, in which acts of violence are committed – whence the name 'haschaschins,' or assassins, applied to the unfortunate hashish-eater who, under the influence of the drug, commits murder… Dilatation of the pupil, and disorders of vision, which contribute to the hallucinations by distortions of external objects, are produced by hemp"

A Practical Treatise on Materia Medica and Therapeutics, by Roberts Bartholow, published in 1893
"There is often a disposition to laugh, sing, shout, or dance, or to do some other extravagant act; but, in other instances, the excitement betrays itself in a quarrelsome temper or deeds of violence… Occasionally, a species of intoxication is induced, with hallucinations or complete delirium… Among those who use it habitually, it is said ultimately to impair the mental faculties"

A Treatise on Therapeutics, and Pharmacology, or Materia Medica, by George B. Wood, published in 1868

The first paper to link cannabis and psychosis was published in 1845 by Moreau de la Tour, a French psychiatrist: https://www.preventteendruguse.org/
https://archive.org/details/duhachischetdela00more/page/n6

Although I welcomed the comments about cannabis made by Tony Blair just before the election, and his recognition of the dangers it poses, I was angered to hear him say to John Humphrys on the Today programme (May 4th 2005), in reference to the down-classification debacle, "It was worth seeing what happened". Was this just some huge experiment conducted primarily on our vulnerable young people? How many of them would, prior to down-classification, ever have been tempted to try the drug but given the "green light" by this government, now find themselves with a psychiatric problem, perhaps for life. We shall never know.

There is much talk about whether cannabis actually *causes* psychosis or schizophrenia. There are 2 points about this argument.

Firstly, to quote from the Report of an ARF (Addiction Research Foundation)/WHO scientific meeting in Toronto as long ago as 1981 on adverse health and behavioural consequences of cannabis use. "It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, "risk-factors" have been freely identified, although full causality has not yet been established. Nevertheless such risk-factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is not often applied to cannabis". …. "To provide rigid proof of causality in such investigations is logically and theoretically impossible, and to demand it is unreasonable".

And in March 2006, Harrison Pope, a professor of psychiatry at Harvard Medical School, said that in most aspects of science, the only way to answer a question once and for all is to do a randomized, controlled trial

of 100 people or more. But since giving people marijuana in a clinical setting poses a rather formidable dilemma he and other psychiatrists must fall back on messy methodology.

Secondly, there is ample undisputed evidence that cannabis exacerbates the course of schizophrenia and triggers it at an earlier age than would have been the case. It also causes a toxic psychosis recognized as a diagnostic unit in the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders.

When you have young people suffering from a psychiatric illness, that would never have manifested itself if he or she had not taken the drug, then cannabis is certainly a contributing factor, whether or not they may have had a genetic predisposition. As new studies emerge, the evidence that cannabis may actually *cause* schizophrenia becomes ever stronger, see the most recent in the updated section at the end of the chapter.

Robin Murray and John Witton of The Institute of Psychiatry, London, in their paper, "Reefer madness revisited: cannabis and psychosis" March 2004, said, "The public health message is clear. Some cases of psychotic disorder could be prevented by discouraging cannabis use, particularly among psychologically vulnerable youths, with the youngest cannabis users most at risk…..action is needed to avoid a further burden on already over-stretched mental health services".

When BSE became a problem, in spite of the fact that the government had no real idea how the disease was transmitted, beef-on-the-bone was banned. "We must err on the side of caution", said a spokesman at the time. Indeed we must. Why were they so incautious in the case of cannabis classification?

It is ironic that the USA whose drug tsar John Walters' strong prevention messages are seeing a consistent year-by-year drop in drug use, invited a British scientist, Professor Neil McKeganey, Professor of Drug Misuse Research, Glasgow University, to speak at a conference on May 3rd 2005, when our previous Home Secretary, David Blunkett, before down-classification, consistently refused to see a group of 6 eminent British scientists, all experts in the field of drugs.

In 2004 I was asked to speak to a group of parents, all of whom had children who were psychotic or schizophrenic. All the youngsters had previously used cannabis. There was no doubt whatsoever in the minds of these parents what had caused their children to become ill. They were incensed that no one had ever warned them of the dangers of this harmful drug. They kept me talking and answering questions for 3 hours. I think it was one of the most emotional and disturbing evenings I have ever spent.

There has been a 22% increase in the number of hospital admissions of cannabis users with mental illness since down-classification in the UK. In the year April 2003-04, the number of admissions was 710, up from 580 in each of the two previous years. In the same period, admissions caused by the abuse of other drugs including heroin and alcohol fell. The exception was cocaine which rose by 16%. I thought that one of the reasons for down-grading cannabis was to free up police time to combat the harder drugs. On April 25th 2008, in answer to a parliamentaruy question from Graham Brady MP, updated figures for admiision to hospitals with mental illness were given. In 2003/4 40,763 people in England were admitted for primary or secondary diagnoses of schizophrenia, in 2006/7 it was 45,955, an increase of 12.7%. For psychosis, the increase was 20.8%, from 176,776 to 213,624. Since 2001, the year in which the intention to downclassify was suggested, the figures for schizophrenia have risen by 24% and those for psychosis by 42%.

On January 23rd 2005, The Herald (Scotland) reported that numbers of hospital discharges after treatment for cannabis-related problems had more than trebled in The Lothians and doubled in the Greater Glasgow Health Board Area. According to police figures, the number of under-16s at the end of 2004 charged with supply or possession of drugs had risen by 13%. Some were only 10 years old.

Professor Peter Jones of Cambridge University, one of Britain's leading psychiatrists and an expert in schizophrenia, addressing an Institute of Psychiatry (London) Conference on 28th November 2005 said, "Cannabis is a huge issue for psychiatric services at this moment. I work in a first-contact schizophrenia service and it might as well be a Cannabis Dependency Unit". He warned that children of 10 or 11 who start smoking the drug could be trebling their risk of schizophrenia. He said that 80% of first episode psychiatric disorders, schizophrenia or schizophrenia-like illnesses occurred in either heavy users of cannabis or cannabis dependents. " I think this is an iceberg effect", he said, "If you were able to measure the toll on GCSE results, A level results, training and social development, we would have a much bigger number of deleterious effects".

Professor Robin Murray of the Institute of Psychiatry in London, who has done so much to draw attention to the links between cannabis and mental illness, took part in a Radio 4 You and Yours programme on 30th December 2004. When asked if he would say that cannabis is one of the biggest problems facing psychiatric wards, replied, "I've been saying it for some time. It's worse now, it's *very* difficult to convince patients that cannabis is causing their problems. They say that's not what the *government* says. Their general understanding is that it is safe".

He ended the programme by saying that Mental Health Services are overwhelmed. People are arriving with cannabis psychosis. They don't get good treatment, nor do these with problems unrelated to cannabis. Mental Health Services in big cities cannot cope. He had recently talked to 100 psychiatrists and asked whether any of them would invite relatives or friends in to see their units. Only *one* would be prepared to do this. "We are awash with mental health problems" he said, " and cannabis is a big contributor".

In a letter to The Guardian 19th January 2006, Professor Murray said, "The mistake was that in its 2002 report, The Advisory Council on the Misuse of Drugs denied that cannabis was a contributory cause of schizophrenia, continued to deny this for the next two years and thus mislead ministers into repeatedly stating that there was no causal link between cannabis and psychosis". On 8th October 2006, he said, "Five years ago, 95% of psychiatrists would have said that cannabis doesn't cause psychosis. Now, I would estimate that 95% say it does. It's a quiet epidemic".

On November 4th 2006 The Manchester Evening News carried a report that "Cannabis raids help patients". Mark Holland, a senior health worker of 26 experience in the NHS as a consultant nurse and senior member of the Manchester Mental health and Social Care Trust, said, " I have definitely noticed a change in many of my clients. …I tell them their symptoms seem a bit milder because they haven't had a joint" Across Manchester there has been a drop in the number of people needing hospital treatment for acute psychotic episodes – one of the first falls in several years. Greater Manchester Police have been taking part in Operation keymer, set up to target hundreds of cannabis factories across the country, focusing particularly on the powerful "skunk" variety.

BBCNews carried a story on May 7th 2007 that admissions to mental health hospitals in England due to cannabis use had risen by 85% between 1996 and 2006. I 1996/7 there were 510 admissions, this rose to 946 in 2005/6. This was given in an answer to a parliamentary question from Andrew Lansley, Shadow Health Secretary. In the last 5 years alone, the rise was 65%. "This is the tip of the iceberg" said Professor Murray. He added that cannabis use was a contributory cause of up to 10% of cases of schizophrenia yet this was unrecognized.

I have therefore attempted to make a list of scientific studies on cannabis and psychosis and to make it available to anyone with an interest in this important subject.

The following list is not in any way meant to be comprehensive. As I researched this subject more and more thoroughly I uncovered literally dozens of other publications. I think I have mentioned all of the most important ones, apologies to the authors of those I have not included but the literature and messages are there for anyone to access.

In the last few years increasing concern has been expressed about the association of cannabis with mental illness. The number of cannabis users is going up. In the USA in some age groups, almost as many people are smoking cannabis as cigarettes. Children are starting to use the drug at an increasingly early age, more and more studies are emerging which link cannabis use with psychological and social problems, demand for treatment for cannabis users is rising and there is a change in the THC content of some cannabis varieties. Selectively bred strains such as skunk and nederwied (netherweed) have much greater percentages of THC than did the marijuana of the sixties and seventies.

Jan Ramstrom, the Swedish psychiatrist and expert on substance abuse who wrote Adverse Health Consequences of Cannabis Use (2003) said, "At present we find ourselves in a curious situation where researchers and clinicians are becoming even more concerned, while the general public, not least in Europe, seems to grow less concerned".
He also said, "It is worth mentioning that the opiates (heroin etc), apart only from the development of dependence, produce far fewer toxic psychiatric complications than do cannabis preparations"

Two fundamentally different psychotic manifestations are involved.

Toxic psychosis: Cannabis-induced psychotic disorder, recognized as a diagnostic unit in the DSM 1V (Diagnostic and Statistical Manual of Mental Disorders) is caused by the toxic effects of the drug and involves a group of brain damage syndromes. The symptoms are caused by cannabis consumption and subside when drug use ceases. The use of anti-psychotic medicines to eliminate any residual symptoms means most patients make a full recovery unless he or she resumes the taking of cannabis or indeed other drugs. Symptoms of delirium often dominate, i.e. bewilderment and memory disturbance. Paranoia, hallucinations and aggression alternating with euphoria also occur. There is usually an absence of any heredity factor.

Functional psychosis: "Functional" in this sense applies to the absence of organic damage. Cullberg 2000, said that there probably is some organic damage, possibly taking the form of some subtle vulnerability as yet unknown. This category covers schizophrenia and schizophrenia-like psychosis which usually runs a chronic course. Symptoms of delirium are absent and there is often a feeling of outside interference with thought. Often the person has a "premorbid personality" with extreme reserve, loss of interest and bizarre suspicious ideas.

To quote Jan Ramstrom again, "…what we are dealing with here are the most profound disturbances known to psychiatry; even when they are short-lived, such disturbances can leave marks on those affected and on their families which may remain for many years or even be of life-long duration…..there is both an abuse condition and a serious mental disorder. These "dual disorders" are among the most difficult to assess in the whole of psychiatry. Moreover, conditions of this type not rarely make demands on the most costly resources available in the field of psychiatric care".

French psychiatrist, Moreau de Tours 1845, first reported acute psychotic reactions in himself, students and patients after taking cannabis. Some of these were short-lived, lasting a few hours but some up to a week.

Early Studies.

Papers as early as the 1970s saw researchers connecting cannabis consumption with psychosis.

1972. Tennant and Groesbeck studied American soldiers in Europe and found large numbers abusing drugs mostly hashish. Between 1968 and 1971, the number of acute psychotic reactions, not necessarily leading to schizophrenia increased from 16 in 1968 to 77 in 1971, an almost 5-fold increase in 4 years. They concluded that hashish smoking was the major contributor.

1974. Chopra and Smith described 200 patients admitted to a Calcutta psychiatric hospital between 1963 and 1968 with psychotic symptoms following cannabis use. Most cases were preceded by the ingestion of large quantities. One third had no previous psychiatric history and the symptoms were the same regardless of their history. The most potent cannabis preparations resulted in psychotic reactions in the shortest period of time.

1974. DA Treffert allowed 4 schizophrenic patients, all on anti-psychotic medicine to act as their own controls. Having been warned not to, all of them smoked cannabis occasionally. All of them experienced deterioration in their condition, sometimes with very serious consequences. This clearly demonstrated that there was a direct association between relapses into pot smoking and serious deterioration in the schizophrenia condition.

1974. Breakey and others pointed to some sort of association between drug use, including cannabis, and the onset of schizophrenic illness. He considered that cannabis and other drugs could precipitate latent schizophrenia, but also thought that cannabis could do this in cases where the illness would not occur otherwise. They based this conclusion on the fact that the drug induces schizophrenia on average 4 years earlier than the onset in other types of schizophrenia. The onset was also more sudden, and the premorbid personality always better than a comparative group of non-drug using schizophrenics.

1976. Thacore and Shukla made a clear attempt to demonstrate the occurrence of a specific cannabis-provoked functional psychosis.

Other papers around this time, giving support to the findings include, Talbott and Teague 1969, Weil 1970, Bernardson and Gunne 1972 and Harding and Knight 1973.

So even as long ago as the early seventies some researchers were trying to ring alarm bells about the

possible psychological problems of cannabis use.

The eighties brought another crop of papers on the subject.

1981. MB Holmberg found that 10% of 16 year-old consumers of large quantities of drugs, almost exclusively cannabis, by the age of 27, would have a record of psychosis. This was much higher than the 3% in the normal population.

1985. Bier and Haastrup looked at psychological admissions over one year in a Copenhagen hospital. Thirty patients had cannabis-provoked psychosis. They then estimated that 15 in a population of 100,000 would be admitted each year with psychosis either precipitated or caused by cannabis.

1986. Negrette and others concluded that interaction between cannabis smoking and schizophrenia had the following characteristics. Cannabis smokers have more relapses, more hospital visits, the positive symptoms of schizophrenia are more dramatic and the patients are less susceptible to neuroleptic medication.

1986. Ghodse said there was clear evidence from countries where heavy cannabis use is common, that cannabis causes a short-term toxic psychosis. This was supported by laboratory experiments.

Among the large body of reports from researchers and clinicians at this time are the following: Palsson, Thulin and Tunving 1982, Rottamburg et al 1982, Tsuang et al 1982, Carney 1984, Brook 1984, Tunving 1985 and Hollister 1986.

However the most important publication at this time was the large study of Swedish conscripts by Andreasson, Allebeck et al in 1987.

Forty-five thousand conscripts had their drug-taking details taken at entry, aged 18 or 19. The levels of schizophrenia were then recorded over the next 15 years. Those on admission who claim to have taken cannabis on more than 50 occasions were found to be 6 times more likely to be diagnosed with schizophrenia in the following 15 years than those who had never consumed the drug. When confounding factors were taken into account, the risk became smaller but remained statistically significant.

Although the study attracted some criticisms, Negrette, the doyen in this field judged the connection to be reasonable taking other previous studies into account, while accepting there were some weaknesses. Andreasson in 1989 and Allebeck in 1993 strengthened their position by further research. They examined the medical records of 112 cannabis-dependent and schizophrenic patients. The findings in all significant respects confirmed the original study.

Further support came from the analysis of records of 100 schizophrenic patients between 1973 and 1977 randomly chosen by Dalman et al in 2002. A large measure of consistency was established with respect to regions, hospitals and timescale as well as the diagnostic criteria for schizophrenia, DSM-1V.

Over twenty years later in 2002, Zammit and others re-analysed the results. In the light of new research into the development of schizophrenia, they were able to discount more of the original objections.

Research continued in the nineties.

1990. Tien and Anthony conducted an epidemiological analysis of drug and alcohol use and concluded that there was an association between cannabis use and psychosis. Daily use over a year suggested a 2.4 times greater risk than non-users, any use related to a risk of 1.3 times. The daily risk figure remained significant after adjustment for other substance abuse and baseline psychiatric diagnosis.

1991. Chaudry et al studied cannabis psychosis following bhang ingestion. Bhang drinkers in Pakistan were found to have mania and paranoid features. Treated with anti-psychotic medicines, the majority recovered completely in 5 days. None had residual symptoms.

1991. Johnson, from his own long experience and a review of the current literature, estimated that 10% of all of those who had used cannabis more than once, experienced either delirium or psychosis. Later estimates confirmed this figure, notably Thomas in 1996 who sent questionnaires to young New Zealanders. Johns as recently as 2001 supported this claim.

1995. Wylie observed a group of British consumers of Dutch cannabis with a high THC content. He recorded a “wave of psychosis and confusional states”. The risk therefore becomes greater the more often cannabis is used and the greater its strength.

1998. Hall concluded that cannabis can cause psychotic like symptoms during intoxication, can lead to a “cannabis psychosis” to increase the relative risk of schizophrenia, and affect the clinical course of established schizophrenia.

Other studies which deserve mention are: Thornicroft 1990, Eikmeir et al 1991, Mathers et al 1991, Rolfe et al 1993, Kristensen 1994, McBride and Thomas 1995, Castle and Ames 1996, Hambrecht and Hafner 1996 and Fowler 1998.

A paper by J Giedd et al in 1999 on development of the adolescent brain must be mentioned here. They conclude that the brain does not finish its development till the mid twenties or beyond. So the warning is that drug abuse could alter the normal course of the maturing of the brain in the teenage years. Research by Giedd on this subject is on-going.

Since the year 2000 there has been a flood of publications.

2000 Wilson et al looked at brain morphology and early marijuana use. *Results*. There are three primary findings related to age of first use of marijuana. Subjects who started using marijuana before age 17, compared to those who started later, had smaller whole brain and percent cortical gray matter and larger percent white matter volumes. Functionally, males who started using marijuana before 17 had significantly higher CBF than other males. Both males and females who started younger were physically smaller in height and weight, with the effects being greater in males. *Conclusions*. These findings suggest that the age at which exposure to marijuana begins is important. Early adolescence may be a critical period for effects that are not present when exposure begins later. These results are discussed in light of reported effects of marijuana on gonadal and pituitary hormones.

2002 Zammit et al followed up the Swedish Conscript study of 1969/70.

Abstract: *Objective*. An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these uncertainties while extending the follow up period to identify additional cases. Design. Historical cohort study. *Setting*: 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20). *Participants*. 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics. *Main Outcome Measures*. Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage. Results. Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, P<0.001), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, p<0.015). the adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases. *Conclusions*. Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.

2002. Louise Arsenault et al assessed 1100 New Zealand children at 11, 15, 18 and 26. Young adults smoking cannabis at the age of 15 were at a greater risk of developing schizophrenia or a schizophrenia-like illness by the age of 26. The risk was 10% times compared to 3% for non-users. Use at 15 was a stronger risk factor for schizophreniform disorder than use by the age of 18.

2002. The Nemesis Study by Van Os et al studied 4045 psychosis-free Dutch people and 59 who had a psychotic disorder, taken at random from 60 localities. They concluded that it must be considered proven that smoking cannabis can provoke a functional (non-toxic) schizophrenia-like psychosis. They replicated

the Swedish study of Andreasson. It was of shorter duration and had fewer participants, but not the weaknesses. There was a baseline assessment and 2 follow up sessions, after 1 and 3 years, by questionnaire and clinical interviews. The study showed that individuals using cannabis at baseline were almost 3 times more likely to manifest psychotic symptoms at follow up. After confounding factors were taken into account the risk remained significant. A dose-response relationship was also found. The risk factor for the heaviest users rose to 6.8.
They concluded: "cannabis use is an independent risk factor for the emergence of psychosis in psychosis-free persons and that those with an established vulnerability to psychotic disorders are particularly sensitive to its effects, resulting in poor outcome".

2002. Nunez and Gurpegui compared 26 patients with cannabis-induced psychosis to 35 with acute schizophrenia. All used cannabis, they were repeatedly urine tested. They concluded that cannabis when continuously and heavily used can induce a psychotic disorder distinct from acute schizophrenia.

2002. Hiroshi Ujike found genetic abnormalities in the genes for the cannabinoid receptors on the brain cells of schizophrenics compared to non-schizophrenics. This implies a potential malfunction of their marijuana-linked circuitry, perhaps making them more vulnerable to schizophrenia.

Many people have argued and it seems logical that if the use of cannabis has increased then so must the incidence of schizophrenia.

2003. Boydell et al found that there was indeed a continuous and statistically significant rise in the incidence of schizophrenia between 1965 and 1997. It had doubled over the last 3 decades. The increase was greatest in people under 35.

2002. In a survey of 3142 prisoners, it was found that, first use of amphetamines or cocaine before the age of 16 and severe cannabis or cocaine dependence were related to an increased risk of psychosis. Severe dependence on heroin was associated with a reduced risk of this classification (Farrell et al 2002).

2003. The Christchurch Health and Development Study. Fergusson et al looked at 1200 children from birth to the age of 21. The cannabis-dependent youngsters developed psychotic symptoms more often than those who were non-dependent. Individuals with cannabis-dependence disorder at 18 had a 3.7-fold increased risk of psychosis than those with no dependence disorder. At 21 the risk fell to 2.3 times.
They conclude that: "the findings are clearly consistent with the view that heavy cannabis use may make a causal contribution to the development of psychotic symptoms since they show that, independently of pre-existing psychotic symptoms and a wide range of social and contextual factors, young people who develop cannabis dependence show an elevated rate of psychotic symptoms".

Another paper on the development of the brain appeared at this time.

2003. Chambers et al reviewed literature regarding the neurocircuitry underlying motivation, impulsivity and addiction. They focused on studies investigating adolescent neurodevelopment.
They found that adolescent neurodevelopment occurs in brain regions associated with motivation, impulsivity and addiction. These developmental processes may advantageously promote learning drives for adaptation to adult roles but may also confer greater vulnerability to the addictive actions of drugs. This has significant implications for understanding adolescent behaviour, addiction vulnerability and the prevention of addiction in adolescence and adulthood.

2004. Veen et al. One hundred and thirty-three Dutch patients with schizophrenia were interviewed. There was a strong association between the use of cannabis and an earlier age of first psychotic episode in male schizophrenics. On average they were 6.9 years younger than non-using patients.

2004. D'Souza et al. Various doses of THC were administered to 22 healthy subjects, screened for any vulnerability to schizophrenia. Some of them developed symptoms resembling schizophrenia for 30 minutes to 1 hour. There were no side effects after 1, 3 and 6 months. The study findings go along with several other lines of evidence that suggest a contribution of cannabis and/or abnormalities in the brain cannabinoid receptor system to the pathophysiology of schizophrenia.

2004. Arendt et al. Findings: 1439 heavy cannabis users seeking treatment for abuse problems in Denmark were compared to 9122 abusers of other substances.
Conclusion: Co-morbid psychiatric disorders are common among heavy cannabis users seeking treatment.

Some psychiatric disorders occur more frequently in this group compared to users of other substances.

2005. Isaac and Holloway did their research in PICUs (Psychiatric Intensive Care Units). There was a high rate of cannabis abuse (71.3%) among the PICU population. Patients with cannabis abuse spent longer as their psychosis was more severe. They were also younger at first hospital admission.
The conclusion was that cannabis abusers have more severe psychotic illness especially in schizophrenia. There are additional problems of weight gain.

2004. Frischer et al from Keele University monitored 3% of the population of England and Wales. The number of people using drugs and having mental illness rose by 62% between 1993 and 1998. (230 GP practices were looked at). Men accounted for 79% and women 44%.
The average age affected fell from 38 to 34. The number of cases of 25 to 34 year olds more than doubled. Drug abuse and psychosis were up by 147%, paranoia by 144% and schizophrenia by 128%.
They said, "A long-term, well funded, innovative campaign aimed at publicising the real mental health risks associated with drugs including cannabis needs to be in place as soon as possible".

2004. Stephanis et al looked at 3500 19-year olds in Greece.
Conclusions: These results add credence to the hypothesis that cannabis contributes to the population level of expression of psychosis. In particular, exposure early in adolescence may increase the risk for the sub-clinical positive and negative dimensions of psychosis, but not for depression.

2005 D'Souza and others, in a 3-day double blind randomized placebo-controlled study, injecting 2.5 mg and 5mg intravenous THC, studied the cognitive, motor, behavioural and endocrine effects in 13 stable, antipsychotic-treated schizophrenia patients and compared them with healthy subjects. They found that Delta-9-THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. No short or long-term adverse effects were found.

2005. Favrat et al. Clinical trials of THC on psychomotor function and driving performance were conducted on 8 occasional cannabis users with no history of psychosis. Low doses were used. Two young men reacted badly. One 22 year-old showed severe anxiety and psychotic symptoms 90 minutes later, and was unable to do the tests. The other, also 22, was unable to do the tests for several hours, and experienced very unpleasant symptoms.
The doses were administered under clinical conditions and were much lower than would normally be found in a modern joint. The importance of this research is that oral administration of the THC caused significant psychotic reactions. Oral medicines are becoming increasingly available and doctors should be aware of these findings.

2005. Ferdinand. The "Zuid Holland" Study, a 14 year follow up study of 1580, initially 4 to16 year olds, drawn randomly from the Dutch population. (Because cannabis use is generally condoned in Holland, false negative reports of cannabis use may occur less frequently. This adds to the value of this study). Findings: Cannabis use in individuals who did not have psychotic symptoms before they began using cannabis, predicted future psychotic symptoms, the risk was almost 3 times greater. Also psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use.
Conclusion: The results either imply a common vulnerability with varying order of onset or a bi-directional causal relationship between cannabis use and psychosis.

2005. Van Os et al. Nearly 2500 young people between the ages of 14 and 24, with or without predisposition to psychosis were studied. Adjustment was done for confounding factors such as alcohol, cigarettes and other drugs.
There was a dose-response relationship with increasingly frequent use of cannabis.
Conclusions: Cannabis use in young people moderately increased the risk of developing psychotic symptoms. The risk for onset of symptoms was much higher in young people with a predisposition for psychosis. Predisposition psychosis at baseline did not predict cannabis use at follow up. This rejects the self-medication hypothesis i.e. that psychotic patients take drugs to relieve the symptoms of the illness.

2005. To investigate the overall effect size and consistency of the association between cannabis and psychosis, a meta-analysis from prospective studies was carried out. The pooled odds ration was 2.1 and could not be explained by confounding or reverse causality. Evidence suggests that cannabis is a component cause in the development and prognosis of psychosis, in which mechanisms of gene-environment interaction are most likely to explain this association (Henquet et al).

2005 Henquet investigsted the relation between cannabis use and psychotic symptoms in individuals with above average predisposition for psychosis who first used cannabis during adolescence. 2437 (14-24 years) with/without this predisposition were studied. They concluded that ' Cannabis use moderately increased the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis'.

An Australian study in 2006 tracked 81 young people mostly male in their early 20s, single, unemployed and who were addicted to cannabis. All of them had developed a psychotic mental illness in the previous 6 months. Dr Leanne Hides said, " We found that cannabis use contributes to a relapse in psychotic episodes and then as a result of that they are more likely to use cannabis. Basically they're going around in circles and they can't really win".

2005. Fergusson et al. This was a 25 year longitudinal study of 1055 New Zealand children from birth. Conclusions: "Even when all factors were taken into account, there was a clear increase in rates of psychotic symptoms after the start of regular use, with daily users of cannabis having rates that were over 150% those of non-users. These findings add to a growing body of evidence from different sources, all of which suggest that heavy use of cannabis may lead to increased risks of psychotic symptoms and illness in susceptible individuals".

2005. Caspi et al. have found variants in a gene (COMT) which is involved in dopamine transmission. It was found to moderate the influence of adolescent cannabis use on the development of adult psychosis. One in four people carries this gene.
The research was carried out on 803 men and women born in Dunedin, New Zealand in 1972 and 1973. They were enrolled at birth. The gene comes in 2 variants, methionine and valine, and everyone has two copies of the gene.
If a person inherits 2 methionine types, the rate of psychotic illness is 3%, the normal rate for non-users. However if a person has 2 valine variants, the rate rises to 15% for those who have used cannabis in their teens. Dr Caspi said, "Research has shown that the valine gene variant and cannabis affect the brain's dopamine system in similar fashion, suggesting that they deliver a "double dose" that can be damaging".
A report in The Independent on 13th May 2007 said that experts from The Institute of Psychiatry in London had isolated the gene an hoped that a mouth-swab test as an early warning system for identifying vulnerable youngsters. Dr Marta Di Forti said screening could help parents worried about their children.

Several review articles have also appeared in the last few years.

2001. Johns. Conclusion: "Heavy cannabis misuse leads to the risk of psychotic episodes and aggravates the symptoms and course of schizophrenia. For any psychiatric patient, risk management and care planning is incomplete without a thorough assessment of substance abuse".

2003. Degenhardt and Hall. Conclusion: "Cannabis use does not appear to be causally related to the incidence of schizophrenia but its use may precipitate disorders in persons who are vulnerable to develop psychosis and worsen the course of the disorder among those who have already developed it".

2004. Arsenault et al. A review of 5 papers was undertaken:
The Swedish Conscript cohort, Andreasson 1987 and Zammit et al 2002.
The Dutch Nemesis Sample, Van Os 2002.
The Christchurch Study, Fergusson et al 2003.
The Dunedin Study, Arsenault 2002.
The overall conclusion: "A twofold increase in the relative risk for later schizophrenia. At the population level, elimination of cannabis smoking would reduce the incidence of schizophrenia by around 8% assuming a causal relationship. Cannabis is a component cause for psychosis, part of a complex constellation of factors".

2004. Rey et al. Conclusion: The weight of evidence points in the direction of early and regular use of cannabis having substantial negative effects on psychosocial functioning and psychopathology.

2004. Drewe et al. This article appeared in response to the potential legalization of cannabis in Switzerland. Conclusion: "An increase in consumption would be expected therefore there would probably be an increase in the prevalence of psychosis, not only acute toxic but also chronic psychosis. Schizophrenic psychoses would be expected to be triggered at an earlier age so there could be deleterious consequences not only for

many currently healthy individuals but for disablement pensions".

2004. Raphael and Wooding. Conclusion: "Of primary importance is the fact that cannabis use does have a number of significant associated harms. It is not a soft or safe option and its notable co-morbidity with psychotic and non-psychotic illnesses make it a significant and growing public health issue – a fact increasingly reflected in both the national and international scientific literature".

Other reviews deserving mention include: Leweke et al 2004, Witton and Murray 2004, John Macleod et al 2004 and Smit et al 2004.

In 2004 Marijuana and Madness was published by Cambridge University Press. The editors were, Professor David Castle of The Mental Health Research Unit, Melbourne, and Professor Robin Murray of The Institute of Psychiatry in London.

Twenty-nine contributors to 13 chapters are listed. Many of them have been mentioned in this article. The review from the journal "Addiction" says:

"Each chapter is well written and well presented…There is little doubt that the chapters are expertly written…Marijuana and madness illustrates clearly the benefits of a multi-disciplinary perspective in providing the tools for answering a complex question".

Professor Robin Murray of the Institute of Psychiatry, London, drew attention to the fact in 2003 that recent evidence had demonstrated that THC increases the release of dopamine, thus increasing its level in the brain. Psychotic symptoms in conditions like schizophrenia are mediated by dopamine.

"The Adolescent Brain: A Work in Progress" was published in June 2005 by The National Campaign to Prevent Teenage Pregnancy (USA), Weinberger DR et al. "In sum, a large and compelling body of scientific research on the neurological development of teens confirms a long-held, common-sense view: teenagers are not the same as adults in a variety of key areas such as the ability to make sound judgements when confronted by complex situations, the capacity to control impulses, and the ability to plan effectively. Such limitations reflect, in part, the fact that key areas of the adolescent brain, especially the pre-frontal cortex that controls many higher order skills, are not fully mature until the third decade of life".

In November 2005 a study by Dr Andrew Campbell of the NSW Mental Health Review Tribunal, and a lecturer in psychology at the University of Sidney, found that 4 out of every 5 incurable schizophrenics had used cannabis regularly between the ages of 12 and 21. He studied schizophrenics committed to institutions or ordered to undergo compulsory treatment in NSW over a 5 year period. He warned that it was an epidemic to which we are blind and quoted figures from Britain and the Netherlands showing a base rate of schizophrenia 11 per 100,000 In Wales compared with London and Amsterdam of 60-70 per 100,000. He attributed the difference to the higher rate of cannabis use in these cities by 12 to 21 year olds.

A Danish study just published in The British Journal of Psychiatry, November 2005, by a team from Aarhus Psychiatric Hospital led by Mikkel Arendt, found that almost half (44.5%) of 535 patients taken from the Danish Psychiatric Central Register and treated for cannabis-induced psychotic symptoms, went on to develop a schizophrenic illness, a third developing paranoid schizophrenia. The signs of schizophrenic illness appeared earlier in cannabis users than others with the condition. Only one in six needed no further treatment. They were compared with 2721 people treated for schizophrenia-spectrum disorders who had no history of cannabis-induced illness. Symptoms appeared in male cannabis users at average age 24.6 years compared with 30.7 in the comparison group, with females it was 28.9 compared with 33.1 years,

On November 30th 2005 researchers from Zucker Hillside Hospital, New York, led by Mazar Ashtari and Sanjiv Kumra presented evidence to The Radiological Society of North America (RSNA) at their annual meeting. They used Diffusion Tensor Imaging (DTI), a sophisticated technique measuring the motion of water molecules in the brain to reveal microscopic abnormalities. They found similar abnormalities in the brains of daily adolescent cannabis users to adolescents with schizophrenia. These defects were in a part of the brain still developing during adolescence and associated with the higher aspects of language and auditory functions.
Their findings also suggested that heavy use of marijuana may lead to earlier onset schizophrenia in adolescents genetically predisposed to the disorder.

2005 Semple et al found that: Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia.
In conclusion, the available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.

2006. Barnes et al studied 152 people recruited to the West London First-Episode Schizophrenia Study. Information on mental state, cognition (IQ, memory, executive functions), social function, age at onset of psychosis and self-reported data on drug and alcohol use were collected. Cannabis use and gender had independent effects on age at onset of psychosis, after adjusting for alcohol misuse and use of other drugs. They concluded that "The strong association between self-reported cannabis use and earlier onset of psychosis provides further evidence that schizophrenia may be precipitated by cannabis use and/or that the early onset of symptoms is a risk factor for cannabis use".

In February 2007, more evidence was obtained for structural abnormalities in the brain due to cannabis use. Szeszko et al investigated prefrontal grey and white matter regions in patients experiencing a first schizophrenia episode who also used, or were dependent on cannabis. Twenty of these patients were compared with 31similar patients with no cannabis use, and 56 healthy volunteers. " Patients who used cannabis had less anterior cingulated anterior matter compared with both patients who did not use cannabis and healthy volunteers". They concluded, " A deficit in the anterior cingulated is associated with a history of cannabis use among patients experiencing a first episode of schizophrenia and could have a role in poor decision-making and in choosing more risky outcomes".

The 21st January 2006 edition of the BMJ carried a paper by Fergusson DM et al entitled "Cannabis and Psychosis". It reviewed and brought together the 2 lines of research on this subject, the epidemiological and neuroscientific studies. The summary points were as follows: -

Epidemiological evidence suggests a persistent association between cannabis use and psychosis that is robust to methodological challenges.
Neuroscientific studies show that cannabis may lead to psychosis through effects on the processing of dopamine in the brain.
Taken together this evidence suggests a causal relation in which frequent use of cannabis leads to a greater risk of psychotic symptoms.

The latest review of the evidence linking cannabis to psychosis was published in August 2006 by Degenhardt and Hall. From 6 longitudinal studies in 5 countries they found that regular use of cannabis predicts an increased risk of a schizophrenia diagnosis or report of symptoms of psychosis. These relations persist after control for confounding factors and don't seem to result from the use of cannabis to self-medicate the symptoms of psychosis. A contributory caused relation is biologically plausible because psychological disorders involve disturbances in the dopamine neurotransmitter system with which the cannabinoid system interacts.
They also asked the question, "What are the policy implications of the evidence on cannabis and psychosis? They said, " The observational evidence and biological plausibility of the hypothesis that cannabis is a contributory cause of psychosis is at least as strong as evidence for causal relations between heavy alcohol and amphetamine use and psychosis. On public health grounds there is a good case for discouraging cannabis use among adolescents and young adults". In the conclusion they called for young adults to be informed of the mental health risks, especially early and frequent use. " We must exercise caution in liberalizing cannabis laws in ways that may increase young individuals' access to cannabis, decrease their age of first use, or increase their frequency of cannabis use. We should consider the feasibility of reducing the availability of high-potency cannabis products".

Skosnik and others in October 2006 researching neural synchronization in cannabis users concluded that, "These data provide evidence for neural synchronization and early-stage sensory processing deficits in cannabis use. This finding, along with the observed increased rates of schizotypy in cannabis users, adds support for a cannabinoid link to schizophrenia spectrum disorders".

A paper by Lehrmann and others in December 2006 found similar brain changes caused by different drugs of abuse. The brains of 42 deceased drug abusers were examined. The drugs involved were cocaine marijuana and PCP. The researchers then measured the level of expression of more than 9000 individual

genes in small tissue samples taken from the aPFC (anterior PreFrontal Cortex), a region important in decision-making. Nearly 80% of the drug abuse cases displayed similar alterations in genetic output compared with the controls. For example, genes involved in calcium signaling were turned down while genes involved in lipid and cholesterol-related pathways were turned up. “Our results show that cocaine, marijuana and PCP can alter the function of this critical brain area in similar ways, which could threaten the drug abuser’s ability to make sound decisions”.

An editorial in the Medical Journal of Australia at the beginning of January 2007 (Jorm and Lubman), announced the expenditure of $21.6 million by The Australian Government for a campaign to get the message right to help the public reduce their risk of mental illness and warn of the link with illicit drugs.

Barkus in a review article in The Psychiatric Times, January 2007 concluded that, “There appears to be evidence of substance use (at least cannabis use) as a component cause for psychotic disorders. However it is still unclear whether substance use operates as a causal factor in the absence of underlying biologic vulnerability to psychosis and whether the expression of isolated psychotic symptoms is directly related to clinical psychotic disorders. The evidence for the causal relationship between substance use and psychotic disorders is primarily based on epidemiologic studies; further clinical studies are needed to determine how substance use operates as a risk factor for psychotic disorders. It is possible that this evidence will emerge from the growing numbers of early intervention services worldwide”.

In March 2007, a paper by Dr Matthew Hickman and others warned that by 2010, up to 25% new cases of schizophrenia in Britons may be due to cannabis. In three English cities, Nottingham, Bristol and Southwark in London, the incidence of exposure to cannabis rose fourfold from 1972 to 2002. In the under-18s it rose 18-fold. The increase would be seen earlier particularly among young men. If cannabis use *causes* schizophrenia, these increases would lead to overall prevalence of 29% and 12% respectively between 1990 and 2010. They point out that up till now there is no *proof* that cannabis is a cause of the condition. Some answers would be forthcoming if the projected increase took place.

2007 Kristensen et al found that cannabis abuse for ‘at risk’ groups increased the risk of psychosis. 48 subjects, identified as at risk of psychosis (subsyndromal psychotic symptoms and/or family history) were examined. At one year follow-up, 6 had made the transition, of the 32 who had no/minimal use of cannabis, only 1 had progressed to psychosis. Of the 16 who had cannabis dependence, five converted to psychosis. Conclusion: The results showed a significant association between cannabis use and conversion to psychosis.

The April 2007 edition of NIDA (National Institute of Drug Abuse USA) Notes highlighted 2 papers on the brain development of adolescents by Galvan et al. “Children and adolescents both have an immature prefrontal area, but only adolescents make risky decisions”, said Dr Galvan, “ We speculated that the adolescent brain must be unique in some way that promotes risk-taking”. They hypothesized that the nucleus accumbens (NAc) in the brain might play a complementary role to the OFC’s (Orbitofrontal Cortex) in adolescent risk taking. The NAc alerts and motivates people when there is an opportunity to get something desirable. The OFC moderates these impulses in the interests of safety and longer-term goals. Thus if NAc activity is highly sensitised when the OFC is weak, the drive to act would over-rule the cautious response and more risks would be taken. From their experiment with 13 children, 12 adolescents and 12 adults, they confirmed their hypothesis. The implications are, they concluded that “disproportionate contributions of subcortical systems relative to prefrontal regulatory systems may underlie poor decision-making that predisposes adolescents to drug use and ultimately addiction”.

A research note from Australia published on June 7th 2007, “Does cannabis use lead to mental-health problems?: findings from the research”, concluded that, “it is crucial that emerging evidence about the links between cannabis use and mental health problems is communicated clearly (particularly to those most at risk) and in a way that acknowledges the complexity of the issues involved without obscuring the level and gravity of the risks posed by cannabis use to vulnerable groups” (Buckmaster and Thomas).

An Australian study released in June 2007 indicates that continuous cannabis use increases psychotic symptom severity but not depression symptom severity in schizophrenic patients. 101 patients from 16 to 50 years of age with schizophrenia and related disorders were examined over a 10-month period. Degenhardt and others estimate that daily cannabis users will see an average 3.9 point increase in BPRS (Brief Psychiatric Rating scale) scores in the following month. This indicates a deterioration in their psychotic symptoms compared with patients not using cannabis. “There was no evidence that cannabis was used in response to increased psychotic or depressive symptoms”.

An article in Psychiatric News on July 6th 2007 highlighted a lecture by Dr Nora Volkow, director of NIDA entitled "The Neurobiology of Free Will" at APA (American psychiatric Association)'s annual meeting in San Diego in May. "Addiction and the progressive loss of control over behaviour that seems to accompany the addictive process are the result of changes in multiple regions of the brain. Changes occur initially as a result of the abnormal increase in dopamine that results from use of all drugs of addiction and eventually affect memory and attention, the regulation of impulsivity, and executive functioning". She said, " We have come to see addiction as a disease that involves the destruction of multiple systems in the brain that more or less are able to compensate for each other. When pathology erodes the various systems, you disrupt the ability to compensate, and the addictive disease erodes and destroys the life of the individual".

In July 2007 a paper was published in The Lancet. It was a systematic review of 35 studies into possible links between cannabis and psychotic illness. It caused a great stir in the press coming the week after Gordon Brown had announced another review of the classification of cannabis. It found that cannabis users were 40% more likely to develop a psychotic illness than non-users, with heavy users being more than twice as likely to suffer from a mental illness. The authors, led by THM Moore and S Zammit predicted that 14% of psychotic outcomes in young British adults may be due to cannabis. Professor Robin Murray of The Institute of Psychiatry in London said this estimate may be too low as the cannabis available today is stronger than in the past. He said, "My own experience suggests to me that the risk with skunk is higher" (The Times 27/08/07). They concluded, "…there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life".

A 2-year study by Yucel et al published in August 2007 found, using brain-imaging technology, that opiate-addicted individuals have to make enormous efforts to exercise control over their drug-taking behaviour in the face of adverse health consequences and are vulnerable to relapse. The frontal cortex was working inefficiently, brain cells in this region were less healthy.

September 2007 saw the publication of a paper, "Cannabinoids influence Lipid-Arachidonic Acid pathways in Schizophrenia" by Smesny et al. "Results demonstrate an impact of long-term cannabis use on lipid-arachidonic acid pathways. Considering pre-existing vulnerability of lipid metabolism in schizophrenia, observed effects of cannabis use support the notion of a gene x environment interaction".

2007 Zammit et al found that their results did not support the presence of different effects of cannabis use on schizophrenia according to variation in the COMT gene.

A letter to the editor of The American Journal of Psychiatry in October 2007 from Bowers and Kantrowitz described elevated levels of plasma dopamine metabolites in cases of cannabis psychosis. Three groups were studied in a small sample. Five cases of first admission cannabis-related psychosis showed significantly higher levels of homovanillic acid (24.8ng/ml) than 15 admitted for non-related cannabis psychosis (15.1ng/ml) and 17 non psychotic subjects (9.6ng/ml).

Professor Robin Murray gave a speech at a meeting, "Cannabis and children – complacency is not an option" organized by the group "Talking About Cannabis" (www.talkingaboutcannabis.com) in the Boothroyd Room, House of Commons on October 30th 2007. He said that if THC is injected intravenously into "normal volunteers" then after 10 minutes delusions and hallucinations would occur, returning to "normality" at about 200 minutes. Volunteers said, "…I thought I was God", "I thought you were all trying to trick me" and "I felt you could read my mind, that's why I didn't answer…my mind was nude". He said if enough THC were used, hallucinations and paranoia would result. Because the THC content in cannabis commonly used by children was much higher now (traditional was 3%, skunk is 14%THC), he said it was not acceptable that 13 year olds were using the equivalent of "a bottle of vodka a day".

He also explained how the balance between two constitiuents of cannabis had changed in the development of skunk. THC causes hallucinations and paranoid ideas but CBD (cannabidiol) is not hallucinogenic, has anxiety-relieving properties and no adverse effect on cognition. In other words it acts as a balance to the THC. In the old herbal cannabis the two ingredients were more or less balanced. Now in the case of skunk, the THC content has been greatly increased and the CBD has not altered, so the relative amount of CBD compared to THC is much smaller. In a report by The Home Office in 2008 about cannabis potency, it was found that cannabis resin had a meanCBD content of 3.5% (Range 0.1 to 7.3%) but in nearly all cases the CBD content of herbal cannabis was less than 0.1%.

He made an important observation, "By accident the controversy over the reclassification of cannabis

provided an opportunity for unofficial public education. This has resulted in a fall in use. What we need now is a proper education campaign aimed especially at children".

A paper in April 2008 by Morgan and Curran took up this theme. Hair analysis was used to determine levels of THC and CBD in 140 drug users. 54 were positive for cannabis. 26 had both THC and CBD present and THC alone in 20 others. Among the 3 groups, THC alone, THC + CBD and no cannabinoid, the THC only group had significantly higher scores for psychosis proneness than the others. The THC+CBD group had significantly lower scores with social withdrawal than the no cannabinoid group. Delusional thinking also scored highly in the THC group and greater than no cannabinoid in the CBD+THC one. This research highlights the importanceof distinguishing between different cannabinoids, and the debate over cannabis-psychosis links.

Cannabis use and adult ADHD symptoms were investigated in a paper by Fergusson and Boden in 2008. The conclusion was, 'The current study suggested that the association between cannabis use and adult ADHD symptoms was mediated by other substance use that was associated with cannabis use. The results suggest that cannabis use leads to other drug use, which in turn leads to increased ADHD symptoms. However it should be noted that the potential influence of such factors as genetic predispositions may still be unaccounted for'.

Cannabis use and brain structural alterations were found in first-episode schizophrenia by Bangalore et al in January 2008. There was a decrease in gray matter density in the right posterior cingulated cortex . Cannabis use may be associated with altered brain structure in particular regions rich in CB1 receptors. A call was made for larger prospective studies.

2008 Feb Ashtari found that adolesceants and young adults who are heavy users of cannabis are more likely to have disrupted brain development. These were found in the memory, attention, decision-making, language and executive functioning skills areas. Subjects had an average age of 19.DTI (Diffusin Tensor Imaging) found an arrest in the developing of the myelin sheath. This could slow signaling in the brain and affect cognitive functioning. Ashtari emphasized the preliminary nature and said it neded more research.

Excessive loss of brain volume was found in cannabis using first episode schizophrenia patients by Rais et al in April 2008. Gray matter volume in the cerebrum reduces over time in schizophrenics. A study involving 51 patients with recent onset schizophrenia were compared with 31healthy subjects. 19 of the patients used cannabis, but no other illicit drug in the 5-year follow-up period, the other 32 used no drugs. By using MRI scans it was found that schizophrenia patients showed a larger gray matter decrease than the healthy controls, also larger increases in lateral and third ventricle volumes then healthy subjects and patients who did not use cannabis in the follow-up period. The decrement was considerably more pronounced in the patients who continued to use cannabis. They concluded, "First episode schizophrenia patients who use cannabis show a more pronounced brain volume reduction over a five-year follow up than patients with schizophrenia who do not use cannabis".

2008 Crebbin et al investigated drug and alcohol misuse in first-episode psychosis in the UK. Information on patients in Northumberland between 16 and 36 years of age was collected at first presentation and annual follow-up from 1998 till 2005. Hospitalisation was used as an outcome measure and violence rates were examined in retrospect. Drug misuse without alcohol was associated with a highly significant increase in hospital days. Alcohol problems with/without co-existing drug misuse was not predictive of increased hospital days. Drug and alcohol misuse together was associated with violence. They concluded that drug misuse may have a bigger impact than alcohol use on the outcome of first episode psychosis. (Drugs were, skunk, amphetamines and cocaine).

June 2008, in a paper by Miettunen and others, adolescents in Finland were found to have an association between cannabis use and prodromal symptoms of psychosis. 6330 children between 15 and 16 were investigated, the largest ever study of its type. Those who had tried cannabis (5.6% of the sample) were more likely to present 3 or more prodromal symptoms after controlling for confounding factors like behaviour. A dose-response effect was seen. " We conclude that cannabis use is associated with prodromal symptoms of psychosis in adolescence".

Leweke 2008 found 'recent replication studies indicate that frequent cannabis use doubles the risk for psychotic symptoms and schizophrenia'.

2008 June, Yucel and others found brain abnormalities in long-term (>10years) and heavy users (>5

joints/day) of cannabis, average age 39.8 years and mean duration 19.7 years, with no history of polydrug use or mental problems. Cannabis users had bilaterally reduced hippocampal and amygdale volumes. Conclusion: "These findings indicate that heavy daily cannabis users across protracted periods exerts harmful effects on brain tissue and mental health".

2008 Zammit et al conducted a systematic review of the effects of cannabis use on the outcomes of psychotic disorders. Cannabis use was consistently associated with increased relapse and non-adherence, but some confounders particularly alcohol had not been accounted for in some studies. They concluded, "Confidence that most associations reported were specifically due to cannabis use is low. Despite clinical opinion, it remains important to establish whether cannabis is harmful, and what outcomes are particularly susceptible, and how such effects are mediated. Studies to examine this urther are eminently feasible". [Two co-authors had been co-opted on to the ACMD in their review of cannabis (PB Jones and TRE Barnes) and several had received fees for lectures, talks or consultancy work for pharmaceutical companies].

2008 Atakan Z. asked if the use of cannabis by people with severe mental illness was important. She said that cannabis use is more common among people with severe mental illness than in the general population. "It has detrimental effects on the course of the illness, physical health and social life of others, as well as being a financial burden on health services". Her article seeks to find out why they continue to use it despite the effects on their condition.

2008 July Lewis et al found that alterations in a molecular pathway activated by marijuana may contribute to the cognitive symptoms of schizophrenia. Expression of the receptor CB1R (cannabinoid receptor in the brain) is significantly reduced in schizophrenics. This results in the transmission of GABA, a neurotransmitter involved with working memory being impaired. Activation of the receptor by THC will worsen this deficit.

August 2008 Spanish researchers have found a strong and independent link between cannabis use and earlier onset psychosis. Gonzalez-Pinto et al said it was not related to gender or the use of other drugs, but to the amount of cannabis used. They estimate that cannabis use accounts for 10% of psychosis cases. Compared with non-users age at onset was reduced by 7, 8.5, and 12 years among users, abusers, and dependents respectively.

2008 August Henquet et al researched gene-environment interplay between cannabis and psychosis. They said that cannabis use is considered a contributory cause of schizophrenia and psychotic illness, but only a small proportion of users develop psychosis. Amount of the drug, duration of using, strength of THC and age of first exposure are all factors. Genetic factors in particular are likely to play a part. "Evidence suggests that mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. In this respect, multiple variations within multiple genes – rather than single genetic polymorphisms – together with other environmental factors)eg stress) may interact with cannabis to increase the risk of psychosis".

2008 September 166 patients in Massachusetts, USA admitted to hospital with bipolar disorder 1 for average 4.7 years were investigated. Patients were more likely to experience a manic or hypomanic episode in the same or subsequent quarter (3 month period) as they had used cannabis than at other times. Baethge et al was the lead German researcher.

Two papers on brain function have been published by McGuire et al in 2008 and 2009. They involved the administration of THC and CBD. FunctionalMRI scanning and behavioural measures were used in healthy male volunteers. Each subject was scanned at monthly intervals on 3 occasions preceded by administration of either THC, CBD or a placebo. In the first paper in 2008 they found that THC reduced activation in the part of the pre-frontal cortex that is normally critical for inhibiting a response. In the second one in 2009, anxiety was tested using faces with fearful expressions. Normally these would provoke anxiety, activate the amygdala and increase skin conductance. CBD reduced the response of the amygdale to the faces and this was correlated with its effect on skin conductance.

2008 November Arendt et al " People who have long-lasting (48 hours) psychotic episodes after smoking marijuana may be exhibiting early signs of schizophrenia". In a previous study, Arendt found that nearly half the people who had an episode of cannabis-induced psychosis went on to develop schizophrenia within the next 6 years. In this study they looked at the genetic roots of both conditions by comparing the family histories of 609 treated for cannabis induced psychosis and 6476 treated for schizophrenia or a related

psychiatric condition. Those treated for cannabis-induced psychosis were found to have the same likelihood of having a 'first degree' relative with schizophrenia as did those treated for schizophrenia. This suggested to the researchers that the 2 conditions are the same. Other researchers have shown that pot-smoking roughly doubles the risk of schizophrenia but it happens sooner if they use cannabis. It looks like it is a gradual process but people should not use cannabis if they want to avoid an increased risk of schizophrenia. Anyone with prolonged period of psychosis after marijuana should seek help early. The sooner it is diagnosed and treated, the better the prognosis. (Based on a nationwide survey of all individuals born in Denmark between Jan 1st 1995 and July 1st 1990 – 2,276,309 people).

2009 Gutierrez et al. 91 in-patients and 192 healthy controls were studied. Results as follows:

In relation to the increased risk of schizophrenia which the interaction between cannabis consumption and *COMT* gene variability might confer, in our study we only found evidence that could support this interaction in the female group and not in the male group. These tendencies did not reach statistical significance, possibly due to a lack of sampling capacity. However, they point in the same direction as the findings of Caspi et al[8] and should be explored in greater depth in a larger sample. New studies along these lines should be developed, ideally in the context of longitudinal designs, in order to clarify, on the one hand, the modulatory role of the *COMT* gene on the risk cannabis poses in the development of schizophrenia and, on the other, on the magnitude of this effect.

2009 Henquet et al studied 31 patients with a psychotic disorder and 25 healthy controls. They found that carriers of the COMT Met/Val allele, but not the Met/Met genotype showed an increase in hallucinations after cannabis exposure. The findings confirm that in people with psychometric evidence of liability, COMT Val/Met genotype moderates the association between cannabis and psychotic phenomena in the flow of daily life.

2009 Aldandashi and Blackman looked at 12 to 17 year olds of both sexes presenting with either mood disorder or psychosis. They found that substance misuse is more likely to cause psychosis than mood disorder and cannabis (42.85%) use more likely than amphetamine (28.57%) or cocaine (14.28%). Alcohol is more likely to produce mood disorders than cannabis.

2009 Morrison and Murray published the results of their experiments carried out at London's Institute of Psychiatry and mentioned previously in this report. 21 healthy male participants (21 to 50) were recruited from staff and students from King's College, London. They had all previously taken cannabis on at least one occasion. They concluded that: 'THC can induce a transient acute psychotic reaction in psychiatrically well individuals. The extent of the psychotic reaction was not related to the degree of anxiety or cognitive impairment'.

2009 Rubino et al looked at early-onset cannabis use and cognitive deficits.

2009 Hickman asked how many cannabis users may need to be prevented in order to prevent one case of schizophrenia (Engand and Wales). The figures he came up with were very large BUT he used data from 1997-1999 – before the huge increase in THC and skunk. So they are not really relevant now. In men 20-24 heavy users it ranged from 2800 to 4700 for 35-39 years old. In women, 20-24, 5470 (25-29) to 10,870 in 35-39s. For heavy use and psychosis men 20-24 1360, to 2480 in women of 16-19. around 2.2 million are thought to use cannabis regularly. If 200,000 men of 20-24 were heavy users it would mean around 70 cases. Schizophrenia is a chronic very serious condition and expensive to treat. Psycyhosis would occur in 147 of them! This is no light matter!

2009 Frisher et al found that the incidence of schizophrenia or psychosis in the general population between 1996 and 2005 had shown no increase. The data was collected from 183 GP practices in England, Wales, Scotland and N Ireland. Almost 600,000 patients each year were investigated, roughly 2.3% of the UK Population aged between 16 and 44. However Professor Robin Murray (Institute of Psychiatry, London, an expert in schizophrenia) criticized the experiment. He said,

"I have known about this study since its inception and advised the authors that they were unlikely to be able to come up with meaningful results. Firstly, a major problem concerns the diagnoses. In my experience GP diagnoses of psychiatric disorders are not very accurate. Secondly, we do not know how many cases of psychosis are dealt with exclusively by psychiatrists and GPs don't know.

The only place with good data on schizophrenia over the years is Camberwell. The incidence has doubled since 1964. Migration accounts for some of that but it has gone up even in the white population. (Boydell et al 2003)

Perhaps more importantly from a theoretical point of view, we estimated that cannabis might account for 10% of all cases of schizophrenia. We do not know what has been happening to the other 90% caused for other reasons.

So I don't think this study tells us much".

The leading researcher Dr Martin Frischer said, "We concentrated on looking into the incidence of schizophrenia during those years and not specifically at cannabis use. "It was relatively low-key research so I don't believe it will re-ignite the debate on whether the drug should be legalised." The research was partly commissioned by the ACMD of which Prof Llana Crome is a member.

Degenhardt et al in 2009 said that "Pot is a risk for psychosis". They conducted a review of the evidence for the relationship. One study found an interaction between marijuana use and a polymorphism of the gene that codes for dopamine. About 25% of the cohort who were homozygous for the polymorphism were nearly 11 times more likely to have developed a shizophreniform disorder than those with the same polymorphism who did not use cannabis. Another study estimated that eliminating all marijuana use would reduce the incidence in the UK by about 8%, "assuming the relationship was causal".

2009 Di Forte et al looked at 280 first-episode psychosis patients who had used cannabis and 174 controls, screened for previous psychotic illness. and recruited in the local PCT area. There was no difference in the cases or controls in terms of cannabis use. However the cases were around 6 times more likely to use daily and nearly 7 times more likely to use sinsemilla or skunk.

2010 A paper from Ontario by Joyce et al on anxiety and mood disorders (AMD) looking at 14,531 adults from 2001 to 2006 provided epidemiological evidence that both light and heavy cannabis use is linked with AMD.

2010 Malone and others looked at adolescent cannabis use and psychosis in a review. They concluded: 'Epidemiological evidence suggests that cannabis use is a risk factor for schizophrenia, while cannabis use in individuals with a predisposition for schizophrenia results in an exacerbation of symptoms and worsening of the schizophrenic prognosis. The neuro-developmental characteristic of adolescence probably creates a more vulnerable circumstance for cannabis to produce psychotic-like symptoms and possibly cause schizophrenia.

2010 March 26th Michael Compton MD, MPH wrote a paper, 'Evidence Accumulates for Links Between Marijuana and Psychosis' for Medscape Psychiatry and Mental Health.
He summarized 2 avenues of research: 1) 'associations between cannabis use and clinical manifestations of psychosis' and 2) 'the biologic plausibility of the observed links'.

1) First: Cannabis is the most frequently abused illegal drug among people suffering from schizophrenia . And in those with psychotic disorders, the initiation of cannabis often precedes onset by several years.

   Secondly: Adolescent cannabis use is more and more being recognized as an independent risk factor for both psychosis and schizophrenia.

   Third: Genetic factors like variants of the COMT gene (normal form met/met) may predispose adolescent users to an increased risk of psychosic disorders. A val/met form of the gene increases the risk in adolescents about fivefold while the val/val increases it around tenfold. The release of dopamine is substantially increased.

   Fourth: Cannabis use before the appearance of psychiatric symptoms may be associated with an earlier age of onset of psychotic and perhaps prodromal symptoms.

   Fifth: A potential association in the general population between cannabis use and schizotypal symptoms or proneness to psychosis is emerging in research studies.

2) First The endogenous cannabinoid (neurotransmitter anandamide) and so the exogenous

cannabinoid THC modulate the release of neurotransmitters including dopamine and glutamate by

interacting with the CB1 cannabinoid receptor in regions implicated in schizophrenia.

Secondly: There is an increased CB1 receptor density in brain regions associated with schizophrenia.

Third: Patients with schizophrenia have raised levels of endogenous cannabinoids in the blood and cerebrospinal fluid.

Fourth: Administration of THC to patients cause both patients and controls to experience transient cognitive impairments and schizophrenia-like symptoms, both positive and negative.

To sum up, it has been suggested that " the endocannabinoid system is altered in schizophrenia and that dysregulation of the system , perhaps induced by exogenous cannabis, can interact with neurotransmitter systems in a way so that a 'cannabis hypothesis' can be integrated with other neurobiologic hypotheses (e.g. those involving dopamine and glutamate)".

He concluded that, " A growing body of clinical and epidemiological research suggests significant but complex links between cannabis use and psychosis. Concurrently, ongoing neurobiologic research is revealing findings in the endocannabinoid system that appear to support the biologic possibility of such links".

2010 May, Foti et al examined the relationship between cannabis use and the course of illness in schizophrenia over 10 years of follow-up after first psychiatric hospitalization. 229 patients were assessed 5 times, at first admission, after 6 months, 2, 4 and 10 years. They conclude: 'Cannabis use is associated with an adverse course of psychotic symptoms in schizophrenia, and vice versa, even after taking into account other clinical, substance use, and demographic variables'.

June 2010 Henquet and others discovered that pot smoking can worsen schizophrenia. Marijuana gives people with schizophrenia a quick rush but worsens their psychotic symptoms within a few hours. 47 healthy people and 48 psychiatric patients were recruited in Holland, they were all regular cannabis users the results showed that the schizophrenics were more sensitive than the healthy individuals to both the positive and negative effects of the drug. These findings help to explain previous findings that show that schizophrenics who smoke marijuana require more hospitalization, respond less well to medication and have more trouble with memory tests. Henquet says it's likely that marijuana triggers schizophrenic symptoms in people who have genetic mutations that sensitize them to the drug's psychotic effects.

2010 Henquet and others investigated the effects of cannabis on psychotic symptoms and mood in patients with psychosis (n=42) and healthy controls (n=38). Conclusions: 'Patients with psychosis are more sensitive to both the psychosis-inducing and mood-enhancing effects of cannabis. The temporal dissociation between acute rewarding effects and sub-acute toxic influences may be instrumental in explaining the vicious circle of deleterious ue in these patients'.

2010 Dekker et al concluded that 'The findings indicate that patients suffering from schizophrenia have associations towards cannabis similar to controls, but they have stronger negative explicit cannabis associations. The strong negative explicit associations towards cannabis could imply that users of cannabis engage in a behaviour they do not imolicitly like. Explicit relaxing expectancies of cannabis might be an important mediator in the continuation of cannabis use in patients and controls'.

2010 Marise Machielsen and others concluded there was a specific association between cannabis use and psychotic symptomatology.

2010 August, De Haan, a psychiatrist from Amsterdam Medical Centre found 60% of youngsters who have a psychosis are smoking marijuana. The risks have increased over the years because the joints are stronger. He says the cases confirm the link that has been established by science.

2010 September Morgan et al investigating the role of cannabidiol found that people who smoke potent strains of cannabis (e.g. Skunk) low in cannabidiol (CBD) are at far greater risk of acute memory loss than people who smoke other types of the drug e.g. hash. 134 users between 16 and 23 were tested for

memory. The researchers found that people smoking cannabis with a low percentage of CBD performed much worse on the memory tests when intoxicated than when they were sober. In contrast those smoking cannabis high in CBD performed just as well on the tests when they were intoxicated as when sober. The amount of THC was identical.

Unbelievably the authors issued some HR advice! 'On the back of this study we believe users should be made aware of the risk of memory impairment from smoking low-dose CBD strains. They should be encouraged to use strains containing higher levels of cannabidiol instead'.

2010 October 8th CBS in the Netherlands (Centraal Bureau voor de Statistiek, Gov institution gathering statistical info about the Netherlands) reported that cannabis use increases the risk for mental health issues. 18,500 people were studied. 4% of 15 to 65 year olds had smoked cannabis in the previous month (more than a quarter reported smoking on a daily or near daily basis). The study found that nearly 20% of male cannabis users had psychological problems compared with nearly 10% of non-users. More than 28% of females had psychological problems versus more than 14% of non-users.

2010 November Staci Ann Gruber, speaking at Neuroscience 2010, the annual meeting of The Society of Neuroscience reported that people who start using marijuana at a young age have greater cognitive shortfalls. Researchers also found that the more marijuana a person used corresponded to greater difficulties in focus and attention. (Teen's brains are only about 80% developed and are not completed till the 20s or 30s).

2010 McGrath and others, using sibling pairs among over 3800 young adults, concluded that 'Early cannabis use is associated with psychosis-related outcomes in young adults. The use of sibling pairs reduces the likelihood that unmeasured confounding explains these findings. This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-relayed outcomes in young adults'.

2010 Stilo and Murray in a review on schizophrenia research said, ' Acute ingestion of cannabis or its active ingredient THCwas found to precipitate acute psychotic episodes in experimental studies, and continuing use of cannabis is known to exacerbate existing psychotic illnesses'.

2010 Skinner et al found among university students in Ireland (Galway) that cannabis use increases the risk of developing psychiatric symptoms, worsened by earlier and heavier use.

2010 Jouanjus et al looked at cannabis-related hospitalizations among 200 patients admitted to the public hospitals of the Toulouse area of France between Jan 2004 and Dec 2007. They found that one of the adverse events (AE) was lethal. Psychiatric disorders occurred in 57.7%, leading to 18.2% of AEs, central and peripheral nervous system disorders, 15.8%, acute intoxication 12.1%, respiratory system disorders 11.1%, and cardiovascular disorders 9.5%.

2011 January. Estrada G and others found more confirmation for the COMT polymorphism interaction with cannabis use. 157young psychiatric patients, mean age 17.01 years, were examined to find out if, a) age at first cannabis use and age at emergence of psychiatric disorders are related and b) such a relationship is modulated by the Val158Met genotype. It was found that those who started using cannabis earlier had an earlier age onset of psychiatric disorders, the distribution of the Val158Met was not different either between diagnosis groups or between cannabis and non-cannabis users. An interaction between Val158Met genotypes and cannabis use was observed specifically on age at emergence of psychiatric disorders with Val/Val genotype carriers showing an earlier age at onset than Met carriers. They concluded that The COMT Val158Met genotype seems to modulate the association between cannabis and age at onset of psychiatric disorders. These results are consistent with previous studies.

2011 Jan Lagerberg et al looked at the onset of bipolar disorder. They looked at 151 patients in treatment with a special focus on excessive alcohol and cannabis use. Patients with excessive alcohol use had a significantly later onset compared with patients with excessive cannabis use, whether it preceded or followed bipolar disorder onset. Lifetime use of cannabis predicted an earlier onset independent of the sequence of onsets. This indicates that an early onset may increase the risk of cannabis use and cannabis use may trigger bipolar disorder in vulnerable individuals.

2011 June. Large et al. published a very important meta-analysis on psychosis and age of onset. They identified 83 studies involving 8167 particpants who used cannabis or other substances and 14,352 who did not. Individuals who used cannabis developed psychosis about 2.7 years younger than those who did not. Those who used any type of substance developed it 2 years younger while in those using alcohol there was no correlation. These findings support the view that cannabis suse precipitates schizophrenia and other psychotic disorders perhaps through an interaction between genetic and environmental disorders by disrupting brain development.

'The results of this study provide strong evidence that reducing cannabis use could delay or even prevent some cases of psychosis. Reducing the use of cannabis could be one of the few ways of altering the outcome of the illness because earlier onset of schizophrenia is associated with a worse prognosis and because other factors associated with age at onset, such as family history and sex cannot be changed. " The results of this study confirm the need for a renewed public health warning about the potential for cannabis use to bring on psychotic illness".

2011 Feb Ashtari et al investigated adolescent brain development particularly on the hippocampus. They looked at 14 (18-20) 'treatment seeking' adolescents with heavy prior cannabis use (5.8 joints/day) after an abstinence of 6.7 months and 14 normal controls. The users showed significantly smaller volumes of the right and left hippocampus compared to controls. So heavy cannabis use after an average 6.7 months abstinence lend support to the theory that cannabis users may impart long-term structural and functional damage. Or the volumetric abnormalities may may present a risk factor for cannabis dependence. These data havepotential significancefor understandingthe observed relationship between earlycannabis exposure at adolescenceand subsequent developmentof adult psychopathologyreported in the literature for schizophrenia and related psychotic disorders.

2011 Feb 23rd Morrison investigated whether cannabis (synthetic THC) elicits schizophrenia – like negative symptoms distinct from sedation. 22 healthy subjects attended 2 sessions in which either THC or placebo was given., random order and double blind conditions. They concluded that 'At plasma concentrations resembling recreational use, THC elicited schizophrenia-like negative symptoms that were not merely attributable to sedation. In the community, negative effects may be an adverse effect of cannabis use'.

2011 Lebel found that in the development of the white matter in the brain, structural changes are still ongoing into young adulthood. 103 healthy people between 5 and 32 were scanned at least twice using MRI. Young adult brains were continuing to develop wiring to the frontal lobe., tracts responsible for complex cognitive tasks such as inhibition, high-level functioning and attention. An important observation was that in some people several tracts showed reductions in white matter integrity over time, which is associated with brain degeneration. Further research is needed to determine whether different clinical disorders like psychiatric disease and neurological disease may be linked to brain structure as the brain ages.

2011 Demirakca et al found that a lower volume in the right hippocampus in chronic cannabis users was corroborated. Higher THC and lower CBDwas associated with this volume reduction indicating neurotoxic effects of THCand neuroprotective effects of CBD. This confirms existing pre-clinical and clinical results. As a possible mechanism the influence of cannabinoids on hippocampal neurogenesis is suggested.

2011 March Compton et al looked at pre-illness cannabis use and the onset of psychosis. 109 first-episode hospitalised patients were studied. 42% of those who had used cannabis daily had an acute mode of onset of psychosis, only 20% of those without prior daily cannabis use had an acute onset.

2011 April, Solowij and others concluded that 'Long-term cannabis use in healthy individuals is associated with smaller cerebellar white-matter volume similar to that observed in schizophrenia. Reduced volumes wee even more pronounced in patients with schizophrenia who use cannabis.
Cannabis use may alter the course of brain maturational processes associated with schizophrenia'.

2011 April Kuepper et al conducted a study into whether an urban environment plays a role in moderating the effects of adolescent cannabis use on psychosis risk. Nearly 2000, 14 to 24 year olds, living in Munich or the rural surrounding were investigated. Cannabis and psychotic symptoms were assessed over a 10 year period. They concluded that exposure to environmental influences associated with urban upbringing may increase vulnerability to the psychotomimetic effects of cannabis use later in life.

2011 Dr Jussi Hirvonen and others in a presentation at the annual meeting of the Society of Nuclear Medicine in San Antonio Texas on 6th June said that imaging scans show that chronic daily use of marijuana can have a detrimental effect on the brain. They found a decrease in the number of receptors involved in a variety of important mental and bodily functions, including pleasure, pain tolerance, movement coordination, memory, appetite and concentration. The brains of 30 chronic daily marijuana smokers were studied over roughly 4 weeks. The CB1 receptors had decreased by around 20% compared to those of the healthy controls who had limited lifetime exposure to cannabis. After a month of abstinence, 14 were re-scanned and the number of receptors were found to have notably increased, suggesting the effects may be reversible. This research has not yet appeared in a peer-reviewed journal. The study was a collaboration between The US National Institute of Mental Health and the US National Institute on Drug Abuse (NIDA).

2011Kuepper R et al concluded that, 'Cannabis use (in adolescence) is a risk factor for the development of incident psychotic symptoms. Continued cannabis use might increase the risk for psychotic disorder by impacting on the persistence of symptoms'. 1923 individuals (German), age 14 to 24 at baseline were studied and assessed 3 times for cannabis use and psychotic symptoms, baseline, 3.5 years (T2) and 8.4 years (T3). The incidence rate of psychotic symptoms over the time, baseline to T2 was 31% in exposed individuals, 20% in non-exposed. From T2 to T3 these rates were 14% and 8% respectively.

2011 October 25th Jones et al found that 'cannabis can cause chaos in the brain'. The nerve activity becomes unco-ordinated and inaccurate. Rats were given a drug mimicking the psychoactive ingredient in cannabis. Co-ordibnated brainwaves across the hippocampus (memory) and prefrontal cortex (planning, decision making, social behaviour) were completely disrupted. The scientists believe the results may help explain the links between cannabis and schizophrenia. Jones said, ' Marijuana use is common anmong schizophrenia sufferers and recent studies have shown that the psychoactive ingredient of marijuana can induce some symptoms of schizophrenia in healthy volunteers'.

2011 Van Winkel et al looked at the AKT1 gene. In Holland and Belgium, 740 non-affected siblings of people with schizophrenia and similar conditions, and 419 controls with no first-degree relatives suffering from such disorders, were studied. Already known was that a gene associated with schizophrenia is AKT1, that cannabis has been associated with these disorders and that siblings of those with psychotic disorders were more likely to develop a psychotic disorder than the rest of the population. They found that the non-psychotic siblings of people with schizophrenia or similar disorders, were twice as likely to be diagnosed with psychotic illness after cannabis use than the general population. The ATK1 gene variation appears to be implicated.

2011 Zammit concluded that 'Cannabis increases risk of psychosis irrespective of underlying COMT genotypes. Thes findings argue against the widely held belief that the risk of developing psychosis following use of cannabis is depebndent on variation within COMT.

2011 September Welch and others found that cannabis use impacts on brain thalamic volumes in people at familial risk of schizophrenia. In the Edinburgh High Risk Study (EHRS), MRI scans were obtained at point of entry to the study and approximately 2 years later. 66 individuals were involved in the study, substance use data were available for 57 of them of whom 25 consumed cannabis between the two assessments. They concluded that there was a significant volume loss bilaterally in the thalamus, more highly significant on the right. These losses remained significant when individuals using other drugs were removed from the analysis.

2011 December Cheetham discovered that cannabis users are born with smaller front part of brain. The orbitofrontal cortex controlling memory, reward and decision-making is 6% smaller in children who go on to smoke cannabis compared with those who don't. This could make them more likely to experiment with cannabis as they may be more impulsive and less capable of calculated decision making. This could act as an early warning system! Scans of 121 12 year olds were taken before they started to experiment, then questioned at 16. 28 admitted smoking pot, 23% less than 10 times. Co-founding factors eliminated, the group had the smaller brains. Other studies on long term users found that the drug seems to affect the size of other areas of the bran. These are normal in children who had smoked the drug so it seems to be regular heavy smoking that is causing the damage.

2012 Blakemore S-J looked at imaging the adolescent brain. She said, ' The past 15 years has seen a rapid expansion in the number of studies using neuro-imaging techniques to investigate maturinational changes

in the human brain. I review MRI studies on structural changes in the developing brain and fMRI studies on functional changes in the social brain during adolescence. These studies point to adolescence as a period of continued neural development. This is an exciting time for developmental cognitive neuroscience, a young field that is set to continue to expand over the next 2 decades'.

2012 Bhattachharyya examined the effects of THC and CBD on regional brain functioning during salience processing. 15 healthy men, occasional cannabis users were given THC, CBD or a placebo on 3 occasions. The aberrant processing of salience is thought to be a fundamental factor underlying psychosis. 'THC and CBD differentially modulate prefrontal, striatal and hippocampal function during attentional salience processing. These effects may contribute to the effects of cannabis on psychotic symptoms and on the risk of psychotic disorders'. There was no significant difference between the cannabidiol and placebo conditions.

2012 April 29th (Italy – 3rd Biennial Schizophrenia International Research Conference in Florence) O'Donoghue found that obstetric complications had the strongest significant influence on age of onset of psychosis, followed by cannabis.use. A total of 608 patients with first episode psychosis were studied. Five factors were considered – Sex, social class of origin, family history of psychosis, cannabis use and obstetric complications. 19% of patients had a family history of psychosis, 44% had had an obstetric complication. Only 3 of the 5 factors were associated with an earlier onset of psychosis – Being male, a history of cannabis use and obstetric complications. Patients with a history of cannabis use had a median age of onset of 22.8 years, obstetric complications was 24.6 years and being male, 26 years.

Dr Mary Cannon, Dublin, said 'Without these risk factors your age of onset is about 30, but if you have 2 of them, this drops to about 20. That amounts to 10 years of very significant life…'

2012 Jan 12th Lynch et al looked at 'The Cannabis-Psychosis Link'. Several findings are interesting:

1. More than 16m Americans regularly use cannabis, typically beginning in adolescence. In the USA, 4% of cannabis users have a diagnosis of either cannabis abuse or dependence, but in schizophrenics the proportion of people with a co-morbid cannabis use disorder is 25%. Cannabis use disorders are especially common in younger and 1st episode patient samples and in samples of high proportions of males.
2. THC interacts with the dopamine (pleasure neurotransmitter) system. Dopamine, which provides a pivotal role in mediating the reinforcing effects of most drugs of abuse, is increased. This increased dopaminergic drive could underlie the abusive property of the drug and increase the positive psychotic symptoms induced by THC. (Murray and many others believe that the increase in dopamine is likely to be the cause of the psychosis, those with schizophrenia and psychosis have an excess of dopamine in the brain)
3. Moore et al in The Lancet 2007 in a systematic review surveyed the literature on this topic. The 'psychosis' outcomes required a diagnosis of a primary psychotic disorder or affective psychosis, or the occurrence of delusions, hallucinations or thought disorder during the study period. Results from 7 cohort studies showed a 40% increased risk of psychosis in cannabis users compared with non-users. The data also revealed a dose-response effect – the risk of psychotic symptoms was increased approximately 50% to 200% in those who used cannabis frequently compared with non-users.

4 Age at onset of psychosis and cannabis use: The Dunedin Multidisciplinary Health and Development Study conducted a prospective longitudinal study of adolescent cannabis use, taking into account psychotic symptoms that occurred before cannabis use. The data were compiled from a birth cohort that consisted of 1037 individuals born in Dunedin, New Zealand. Information about psychotic symptoms was obtained at age 11, and drug use was assessed by self-reports at ages 15 and 18 and by a standardized interview schedule at age 26. Two psychosis-related outcomes were measured—the presence of symptoms of schizophrenia and the diagnosis of schizophreniform disorder.

The results showed that those who had used cannabis by ages 15 and 18 had more schizophrenia symptoms than controls, a finding that remained significant after controlling for the presence of psychotic symptoms at age 11. However, the increased likelihood of schizophreniform disorder at age 26 was no longer significant after controlling for psychotic symptoms at age 11. Taken together, this suggests that early cannabis use confers higher risk of psychosis.

2012 Pelayo-Teran et al looked at gene-environment interactions underlying the effect of cannabis psychosis. Abstract: Cannabis use may be considered as an additional risk factor in a diathesis-stress model of schizophrenia where the risk of de-veloping the illness would be higher in genetic vulnerable people. In this regard, much of the research on cannabis and psychosis is cur-rently focusing on gene-environment interactions. The present review will focus on the interaction between genes and cannabis exposurein the development of psychotic symptoms and schizophrenia and the biological mechanisms of cannabis. Cannabis use has been shownto act together with other environmental factors such as childhood trauma or urbanicity producing synergistic dopamine sensitization ef-fects. Studies on gene-environment interaction have mainly included genetic variants involved in the regulation of the dopaminergic sys-tem. The most promising genetic variants in this field are COMT, CNR1, BDNF, AKT1 and NRG1. Additionally, the interaction withother environmental factors and possible gene-gene interactions are considered in the etiological model.

2012 April Whelan et al found in brain scans almost 2000 14 year olds, that some nerve networks don't work so well in some teenagers, making them more impulsive These were in the orbitofrontal cortex, which is involved in decision-making and linked with experimentation with alcohol, cigarettes and illegal drugs in early adolescence, and offer poor inhibitory control. Another separate neural network which is involved with the symptoms of ADHD was NOT connected with this decision-making area. The researchers were able to 'fish out' 7 networks involved where impulses were successfully inhibited, but another 6 when inhibition failed. A genetic variation in a norepinephrine transporter gene was also involved.

2012 Feb Ersche et al looked at the brain'wiring' of 50 biological siblings, one addicted to cocaine or amphetamines, the other with no history of drug abuse. A child of drug-addicted parents is 8 times more likely to become an addict than one in a drug-free home. Self-control was tested. People with poor self-control, including most drug addicts, find it difficult to exercise this. All of the sibling pairs did worse than the 50 unrelated healthy volunteer controls. Brain scans showed that each of the sibling pairs had abnormal interconnections between parts of the brain that exercise control and those involved with drive and reward. Also some individual brain structures were larger – the putamen, responsible for habit-forming, and the medial temporal lobe – learning and memory. The interesting thing is that although the sibling brains were similarly wired (wrongly) one of the pair had not used drugs. So there may be a way of helping vulnerable youngsters.

2012 Feb Anglin et al used prospective data from 804 participants was used to determine associations between early cannabis use and later schizotypal symptoms, accounting for important potential confounds (e.g., adolescent schizotypal symptoms. They found that Cannabis use with onset prior to age 14 strongly predicted SPD symptoms in adulthood, independent of early adolescent SPD symptoms, major depression, anxiety disorder, other drug use, and cigarette use. There was no interaction effect of early cannabis use and early adolescent SPD symptoms on SPD symptoms into adulthood.

2012 May Manrique-Garcia and others found that cannabis-related psychosis may not increase the risk for schizophrenia. They looked again at the 50,000 individuals, military conscripts in Sweden, who had reported their cannabis use since adolescence and over a 35 year period.

'The study revealed that the individuals who used cannabis regularly were almost four times more likely to develop schizophrenia than those who never used cannabis and more than twice as likely to experience a brief psychosis episode. The results also showed that the risk for future psychosis and schizophrenia weakened over the long-term. Manrique-Garcia said, "Of the cases related to cannabis use, 60% occurred during the first decade compared with 45% among non-users of cannabis." However, the findings also demonstrated a clear relationship between dose and risk. In particular, those who used the highest amounts of cannabis for the longest periods of time had the highest risk of schizophrenia. This risk was increased by early episodes of psychosis, regardless of whether they were cannabis induced or not. The individuals who experienced episodes of cannabis-induced psychosis and those who had non-cannabis-related psychotic episodes were equally at risk for schizophrenia. But Manrique-Garcia points out that the individuals with cannabis-related psychosis may not have experienced any psychotic episodes if they had not used cannabis. Further research is needed to determine if this would ultimately decrease their risk for the later development of schizophrenia'.

2012 May. Behan et al looked at adolescent cannabis use and its effects on the COMT gene, first written about in 2005 (Caspi). They used mice whose COMT gene had been 'knocked out'.

Behan said, "This is the first study to show that the combined effects of the COMT gene with adolescent cannabis use cause physical changes in the brain regions associated with schizophrenia. It demonstrates how genetic, developmental, and environmental factors interact to modulate brain function in schizophrenia and supports previous behavioural research which has shown the COMT gene to influence the effects of adolescent cannabis use on schizophrenia-related behaviours' The 3 areas of the brain assessed in this study were found to show changes in cell size, density and protein levels.

2012 October Degenhardt et al investigated the persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. Nearly 2000 children were recruited in secondary school at 15 years of age and surveyed 9 times afterwards. Conclusions: Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety, but not depressive disorder, in adolescence and late young adulthood, even among regular users who then cease using the drug. It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population.

2012 Di Forti et al confirmed that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. 489 first-episode psychosis patients and 278 control subjects were investigated. They concluded that 'Our findings provide strong support for the initial report that genetic variation at rs2404732 of AKT1 influences the risk of developing a psychotic disorder in cannabis users.

2012 Nov, Loeberg et al looked at cannabis use to see if it could lead to schizophrenic breakdown. They found a different brain activity pattern in MRI scans among schizophrenics with cannabis use, than schizophrenics without cannabis use. The 26 patients in the study showed that cannabis use causes a temporary cognitive breakdown in non psychotic individuals leading to long-term psychosis. This implies that the cannabis itself leads otherwise non-psychotic people down the nightmarish path towards schizophrenia by imitating the cognitive weakness that is the main risk factor for developing the psychological condition.

2012 October Moller et al looked at self-harm and substance abuse among 4126 people. They concluded that self-harm in young and middle-aged adults appeared to be associated with current smoking, marijuana and 'dependent' alcohol use. Other independent predictors include younger age, male gender, bisexual orientation, financial strain, education level, psychological distress, adverse life events and sexual abuse by a parent.

2013 Hermens et al found that frequent alcohol, nicotine or cannabis use is common in young persons presenting for mental health care. 2122 young people, aged 12 to 30 provided information as part of a patient register. 3 age groups, 12-17, 18-19 and 20-30 were used. The rates for 'at least weekly use' of alcohol were 12%, 39% and 45%, for cannabis, 7%, 14% and 18%. Rates of daily use of nicotine 23%, 36% and 41%. Age of onset across the 3 substances was approximately 15. They concluded: ' Frequent use of alcohol, nicotine or cannabis in young people seeking mental healthcare is common. Given the restricted legal access, the patterns of use in those aged 12-17 are particularly notable. Reductions in substance use needs to be prioritized within services for at-risk young people.

2013 Jan. Stefanis et al looked at age of initiation of cannabis use and onset of psychosis in 997 participants from the 2010 Survey of High Impact Psychosis (SHIP) in Australia. We tested for group differences in age at onset of psychotic illness and in the duration of premorbid exposure to cannabis (DPEC). The association between age at initiation of cannabis use and age at onset of psychotic illness was linear and significant, even after adjusting for confounders. A temporal direct relationship between age at initiation of cannabis use and age at onset of psychotic illness was detected with a premorbid exposure to cannabis trend of 7-8 years, modifiable by higher severity of premorbid cannabis use and a diagnosis of SSD. Cannabis may exert a cumulative toxic effect on individuals on the pathway to developing psychosis, the manifestation of which is delayed for approximately 7-8 years, regardless of age at which cannabis use was initiated.

2013 Jan. Lev-Ran and others looked at 43,070 respondents aged 18 and above to examine the prevalence of cannabis use and CUDs (Cannabis Use Disorders) in a wide range of mental illnesses.

RESULTS:
Rates of weekly cannabis use, less than weekly cannabis use and CUDs among individuals with 12-month mental illness were 4.4%, 5.4% and 4.0%, respectively, compared to 0.6%, 1.1% and 0.4%, respectively, among individuals without any 12-month mental illness. The odds ratio for cannabis use among individuals with 12-month mental illness vs. respondents without any mental illness was 2.5, and the odds of having a CUD among individuals with 12-month mental illness were 3.2, after adjusting for confounding variables and additional substance use disorders. Cannabis use and CUDs were particularly associated with bipolar disorder, substance use disorders and specific (anti-social, dependant and histrionic) personality disorders. Persons with a mental illness in the past 12months represented 72% of all cannabis users and we estimated they consumed 83% of all cannabis consumed by this nationally representative sample.

CONCLUSIONS:
The current study provides further evidence of the strong association between cannabis use and a broad range of primary mental illness. This emphasizes the importance of proper screening for frequent cannabis use and CUDs among individuals with primary mental illness and focusing prevention and treatment efforts on this population.

2013 January Castle D, 'Cannabis and psychosis: what causes what? Castle looked at the evidence for this and concluded: Applying the cumulative causal factor model, very few "cases" of schizophrenia (estimated population attributable fraction - PAF- around 8%) would actually be "prevented" with the global abolition of cannabis. This low PAF is compatible with epidemiological findings that schizophrenia is a ubiquitous accompaniment of the human condition and rates do not vary very much between cultures and settings despite wide variations in cannabis use. At an individual level, though, it would seem important to educate people at heightened risk of schizophrenia (e.g. through having a family history of the disorder, or having experienced psychosis-like symptoms) of the potential additive causal risk cannabis exposure might bestow.

2013 January Gage SH et al looked at the role of cannabis in schizophrenia. Conclusions:
Despite consistent evidence that individuals who use cannabis have an increased risk of psychotic outcomes, it should not be surprising that the role of cannabis in the aetiology of schizophrenia remains uncertain given the limits of observational epidemiology. In particular, the extent to which the incidence of schizophrenia will be altered by reducing cannabis use or changing the type of cannabis used in the population, or in specific subgroups, remains unclear. Whilst the evidence is "good enough" to continue promoting the public health message that cannabis is harmful, and that it may increase risk of schizophrenia, it is important not to overstate the evidence: the majority of people who use cannabis will not develop schizophrenia, and it appears that a considerable number of heavy cannabis users would need to be prevented in order to prevent one case of schizophrenia. From a scientific perspective, however, the extent to which use of cannabis leads to an increased incidence of schizophrenia, independently of confounding characteristics and separate from effects of chronic intoxication, remains uncertain. Whether preventing cannabis use will have any substantial impact on preventing psychotic disorders in the population, or within specific subgroups at risk, is yet to be adequately determined.

2013 Niemi-Pynttari eta al looked at substance-induced psychosis converting into schizophrenia. Abstract: Using the nationwide Finnish Hospital Discharge Register, we followed all patients (N = 18,478) since their first inpatient hospital admission with a diagnosis of SIP (codes 2921 and 2928 in DSM-III-R and codes F10-F19 in ICD-10 with a third digit of 4, 5, or 7) between January 1987 and December 2003 in Finland. Patients (mean age = 43.7 years, standard deviation = 13.5 years) were followed until first occurrence of schizophrenia spectrum disorder, death, or the end of December 2003, whichever took place first. Conversions of discharge diagnoses into schizophrenia spectrum disorders (codes 2951-2959 and 2971 in DSM-III-R and codes F20, F22, and F23 in ICD-10) were recorded at follow-up. Eight-year cumulative risk to receive a schizophrenia spectrum diagnosis was 46% (95% CI, 35%-57%) for persons with a diagnosis of cannabis-induced psychosis and 30% (95% CI, 14%-46%) for those with an amphetamine-induced psychosis. Although alcohol-induced psychosis was the most common type of SIP, 8-year cumulative risk for subsequent schizophrenia spectrum diagnosis was only 5.0% (95% CI, 4.6%-5.5%). No differences were detected with regard to gender, except for amphetamine-induced psychosis, which converted into a schizophrenia spectrum disorder significantly more often in men (P = .04). The majority of conversions to a schizophrenia spectrum diagnosis occurred during the first 3 years following the index treatment period, especially for cannabis-induced psychosis. Substance-induced psychotic disorders predict schizophrenia spectrum disorders to a greater extent than previously thought.

Allebek 2013 April 7th, revisited the study of male Swedish conscripts around 1969/70. This showed that shizophrenia patients with a history of cannabis use had longer hospital says, higher rate of hospital readmission, and a type of schizo that may be more severe than schizo cases in general. Altho there is increasing evidence of a link etween cannabis use and schizo, unclear whether prognosisand outcomes in these pato=ients differfrom their non-using cannabis counterparts. Over 50,000 male Swedish conscripts between 18 and 19 in 1969/70 were examined and adjusted for confounding factors. Of the conscripts, 5391 used cannabis, 350developed schizo, 58 were cannabis users. The median duration of first hosp admiss was almost twice as long for users as non(59 v 30 days) Athird of users needed more than 90days, only 20% non-users were hosp for that long. Cannabis users had a median of 10 readmissions v 4 for non-users. After controlling for confounding factors, there was a more than 3-fold increased risk of long hosp days in can users, and the no of readmissions was also about 3-fold. He concluded that schizo caused or contributed by cannabis use may be more severe than schizo cases in general Patients + cannabis history seem to have more severe and more persistent history of schizo as indicated by duration of first vist, total duration of hosp days, nos of readmissions

2013 April, Morgan et al found that: 'Anandamide is a ligand of the endocannabinoid system. Animals show a depletion following repeated Δ^9-tetrahydrocannabinol (THC) administration but the effect of

cannabis use on central nervous system levels of endocannabinoids has not been previously examined in humans. Cerebrospinal fluid (CSF) levels of the endocannabinoids anandamide, 2-arachidonoylglycerol (2-AG) and related lipids were tested in 33 volunteers (20 cannabis users). Lower levels of CSF anandamide and higher levels of 2-AG in serum were observed in frequent compared with infrequent cannabis users. Levels of CSF anandamide were negatively correlated with persisting psychotic symptoms when drug-free. Higher levels of anandamide are associated with a lower risk of psychotic symptoms following cannabis use,.

2013 Bosker et al assessed psychomotor function in chronic daily cannabis smokers during 3 weeks continuously monitored abstinence on a research unit. Performance on critical tracking and divided attention tasks was assessed on 19 male daily chronic cannabis users. Psychomotor performance moderately improved over the 3 weeks of sustained abstinence but did not recover to equivalent control group performance. However: The smokers and controls were not matched for education, social economic status, life style and race.

http://www.drugaddictiontreatment.com/types-of-addiction/marijuana-addiction/marijuana-withdrawal-added-to-dsm-5/

Marijuana Withdrawal Added to DSM 5

Posted on July 27, 2013 in Marijuana Addiction, Research & News3

Cannabis-related disorders are a group of mental health conditions that stem from the use of THC-containing marijuana or hashish. The American Psychiatric Association (APA) classifies these conditions as specific examples of a more comprehensive category of problems called substance-related disorders. Cannabis withdrawal, one of the cannabis-related disorders listed in the 2013 edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders,* is a newly defined condition. Another one of the listed disorders, called cannabis use disorder, combines the diagnoses of two conditions—cannabis abuse and cannabis dependence—formerly included as separate mental health issues in previous edition of the *Diagnostic and Statistical Manual.*

Cannabis-Related Disorder Basics

The new *Diagnostic and Statistical Manual* (designated by the American Psychiatric Association as DSM 5) contains definitions for four cannabis-related disorders: cannabis intoxication, cannabis use disorder, cannabis withdrawal and "other" cannabis-induced disorders. Cannabis intoxication is the only one of these disorders that appears in DSM 5 in essentially the same form as it appeared in DSM IV, the previous edition of the *Diagnostic and Statistical Manual.* Cannabis use disorder replaces both cannabis abuse and cannabis dependence. Cannabis withdrawal was created for DSM 5 in recognition of the possible effects of suddenly stopping or heavily reducing habitual marijuana or hashish intake. The "other" cannabis-induced disorders listing replaces several different DSM IV disorders, including cannabis-induced anxiety disorder, cannabis-induced psychotic disorder with hallucinations, and cannabis-induced psychotic disorder with delusions.

Cannabis Intoxication

People affected by cannabis intoxication have typically smoked or ingested marijuana or hashish within roughly two hours of the onset of their symptoms. Specific symptoms that indicate the presence of intoxication include a significant spike in the normal heart rate, mouth dryness, appetite elevation and unusual fluid accumulation in the eyelids (a condition known as conjunctival injection). In addition to at least two of these cannabis-related alterations, all diagnosed individuals must experience substantial psychological or behavioral impairments as a result of marijuana or hashish use. They must also lack other conditions that provide a more reasonable basis for their mental/physical state.

Cannabis Use Disorder

Under the criteria listed in DSM IV, people with significant problems related to their cannabis use who show no signs of physical/mental dependence could receive a diagnosis of cannabis abuse. Examples of problems that qualified as significant include a frequent inability to meet any essential duties or responsibilities, frequent participation in dangerous activities while under the influence of cannabis, and an insistence on continuing cannabis use despite its known harmful life impact. The DSM IV criteria also allowed for a separate diagnosis of cannabis dependence in people who do show signs of physical/mental dependence on marijuana or hashish.

However, modern scientific thinking indicates that the difference between substance abuse and substance dependence is rarely cut-and-dried. In reality, doctors and researchers can find no consistently sensible way to address abuse and dependence as separate issues. For this reason, DSM 5 includes combined listings for specific substance use disorders instead of listings for various forms of abuse and dependence. This means that cannabis abuse and cannabis dependence are now addressed together under the cannabis use disorder heading.

Cannabis Withdrawal

According to the guidelines established by the American Psychiatric Association, substance withdrawal qualifies as a mental health concern when it produces symptoms that significantly degrade participation in a functional routine or trigger troublesome states of mind. Prior to the publication of DSM 5, there was not enough scientific evidence to ascribe these types of effects to withdrawal from the use of marijuana or hashish. However, times have changed, and the APA now officially recognizes the fact that at least some of the people who withdraw from these substances meet the mental health criteria for substance withdrawal. Doctors can now use the cannabis withdrawal diagnosis to identify these people.

"Other" Cannabis-Induced Disorders

Cannabis is known for its ability to produce symptoms in some users that strongly resemble the symptoms of certain diagnosable mental conditions. DSM IV identified two such conditions: anxiety—which produces unreasonable worry, fear or dread—and psychosis, which classically involves the onset of either sensory hallucinations or fixed, irrational beliefs known as delusions. DSM 5 still allows doctors to diagnose these conditions in cannabis users; however, it also acknowledges the fact the cannabis users can potentially develop other mental health problems directly related to their marijuana or hashish use. The "other" cannabis-induced disorders category was created in order to provide doctors with the freedom to specify exactly which issues they uncover in their cannabis-using patients.

Raver et al 2013 investigated whether adolescent cannabinoid exposure alters cortical oscillations in adults. Cortical oscillations are integral for cognitive processes and are abnormal in people with schizophrenia. The endocannabinoid system on which marijuana acts is a neuromodulatory system which actively develops cortical oscillations. They demonstrated that chronic adolescent but not adult cannabinoid exposure suppresses pharmacologically evoked cortical oscillations and impairs working memory performance in adults.

2013 Van der Pol and others compared mental health differences between frequent cannabis users with or without dependence and the general population. They concluded that 'Cannabis use patterns, childhood adversity and the use of other substances are similar in dependent and non-dependent frequent cannabis uses. With the exception of more externalizing disorders, the mental health condition of non-dependent frequent cannabis users is similar to that of the general population, whereas it is worse in dependent frequent cannabis users.

2013 Blakemore, S-J is rethinking the adolescent brain. In an article in The Lancet she documents her research on the subject. She became intrigued by the fact that people with schizophrenia predominantly experience their first episode of psychosis early in adulthood. She found that 'adolescence is not too late in terms of learning, training and intervention. The idea that if something goes wrong in the first 5 years of your life, it's too late to do anything about, is really contradicted by this new research, which suggests that developmental plasticity very much continues'.

2013 Di Forti et al found that daily use, especially of High-Potency Cannabis, Drives the Earlier Onset of psychosis in Cannabis Users. 410 first-episode psychosis patients were studied to investigate the association between gender, patterns of cannabis use and and AOP (Age of Onset of Psychosis). Patients with a history of cannabis use presented with their first episode at a younger age than those who had never used cannabis. This association remained significant after adjusting for gender. Those who started at 15 or younger had an earlier onset than those over 15. Subjects who had been using the high potency cannabis (skunk) every day, had the earliest onset, on average 6 years earlier than non-users.

2013. Poulton, looking at the results of the Dunedin Study (running now 40 years and involving over 1,000 subjects) said that chronic cannabis use in early adolescence makes some people up to 11 times more likely to develop schizophrenia. For people who used cannabis heavily before the age of 18, the risk of schizophrenia went up 10.3%. Heavy usage after 18 increased the risk by 4.7%. He also said that for certain people with a specific gene combination the risk increased about 11 fold, and that a quarter of the population carries this combination.

2013 Van Haren et al looked at brain volume loss in schizophrenia and confounding factors. There is convincing evidence that schizophrenia is characterised by progressive brain volume changes during the course of the illness. It has now been discovered that medication intake and cannabis use are important confounding factors when interpreting brain volume anomalies. Continued use of cannabis but not smoking is associated with a more pronounced loss in grey matter in the anterior cingulated and prefrontal cortex.

Davis et al, 2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC Wave 2). Nearly 35,000 adults in the USA surveyed for cannabis use and psychotic-like symptoms in the first population-based study. The Association between lifetime cannabis use, psychosis and schizotypal personality features was examined. The prevalence of psychosis and schizotypal personality disorder significantly increased with greater cannabis use in a dose-dependent manner. Association for cannabis use and psychosis was 1.27, lifetime abuse 1.79 and lifetime dependence 3.69. There was a similar dose–response relationship for cannabis and shizotypal.

2013 Rocchetti and others questioned whether cannabis is neurotoxic for the healthy brain. 14 studies (362 users and 365 non-users) were looked at for alteration in grey and white matters in non-psychotic subjects. The meta-analysis showed a consistent smaller hippocampus in users compared to non-users. Conclusion: ‘Chronic and long-term cannabis exposure may exert significant effects in brain areas enriched with cannabinoid receptors such as the hippocampus which could be related to a neurotoxic action’.

2013 Issa et al examined the effects of Dronabinol (synthetic THC) on patients to compare them with the effects of whole cannabis. 30 chronic non-cancer pain patients taking opioids but not cannabis were used. 10mg and 20mg doses of Dronabinol were used. These were found to have similar psychoactive effects to smoking marijuana. This risk must be considered when prescribing cannabinoid medications for pain relief.

2013 Hurd et al said that perception of marijuana as a ‘safe drug’ is scientifically inaccurate after lookinfg at 120 teen brain studies. The current evidence suggests that cannabis exposure has a far-reaching influence on adult addictive behaviours particularly for certain subsets of vulnerable individuals. They looked at genetics, environment, brain biology, chemical reactions, gateway and psychosis. Data from epidemiological studies have repeatedly shown that association between cannabis use and subsequent addiction to heavy drugs and psychosis(schizophrenia). The risks are not the same for all of them. Genetic factors, age of initiation and intensity of use are all involve.When cpomparing older and younger adolescents the younger ones are worse in mental health, educational attainment, delinquency and ability to conform to adult roles. A quarter of adolescents will develop an abusive or dependent relationship with the drug.

2014 Smith and others found that regular teenage smokers of marijuana may be at increased risk of schizophrenia. Smoking daily for 3 years resulted in poor performance in tests of working memory and abnormal changes in brain structure akin to those seen in patients with schizophrenia. These changes appeared to last at least a few years after stopping. The marijuana smokers started daily smoking between 16 and 17 and continued for 3 years. At study time they had been free of marijuana for 2 years. They did not abuse any other drugs.

2014 Proal et al, looked at familial morbid risk for schizophrenia is the crucial factor that underlies the association of adolescent cannabis use with the development of schizophrenia. All cannabis-using subjects had used no other drug except alcohol. They concluded: 'Having an increased familial morbid risk for schizophrenia may be the underlying basis for schizophrenia in cannabis users, not cannabis use by itself.

2014 Hartz et al investigated the co-morbidity of severe psychotic disorders with measures of substance abuse. The Genomic Psychiatry Cohort consists of 9142 clinically assessed multi-ethnic sample with various severe mental illnesses. Thee were 10,195 controls. The results were: Relative to the general population, Individuals with severe psychotic disorders have increased risks for smoking, odds ration 4.6, heavy alcohol use 4, heavy marijuana use 3.5,and recreational drug use 4.6. All races (African-American, Asian, European American and Hispanic) and both sexes had greatly elevated risks for smoking, alcohol, marijuana and drug use.

2014 Alemany and others investigated whether the psychotic-inducing effects of cannabis are related to both childhood abuse and the COMT genotypes. 533 individuals were assessed for psychotic experiences, childhood abuse, cannabis use and COMT Val/Met genotypes. Conclusion: Cannabis use after exposure to childhood abuse may have opposite effects on the risk of psychotic experiences depending on the COMT genotypes providing evidence for a qualitative interaction. Val carriers exposed to childhood abuse are vulnerable to the psychosis-inducing effects of cannabis.

2014 Clausen et al did a 5-year follow-up of patients with first-episode psychosis. They found that continuous cannabis use was associated with higher levels of psychotic symptoms after 5 years and this association was only partially explained by insufficiebnt antipsychotic medicine.

2014 Donoghue et al investigated cannabis use and age of onset of schizophrenia. Cannabis users had an earlier age of first symptom than non-users. The gender difference in age of onset was diminished in cannabis smokers compared with non-smokers.

2014 Lagerberg et al investigated a dose-response relationship between cannabis use and age at onset in bipolar disorder. They found a significant association indicating a dose-response relationship between cannabis use and age at onset in bipolar disorder, which remained statistically significant after controlling for possible confounders.

2014 April 15th Gilman et al found brain changes associated with casual marijuana use in young adults. MRI imaging was used to compare brains of 18 to 25 year olds who reported smoking cannabis at least once a week. None were dependent on the drug. The more they used, the greater the damage in 2 regions: the nucleus accumbens (reward processing) was larger and altered in shape and structure compared with that of non-users and the amygdala (emotions) had the same results.

2014 Freeman and others found out how cannabis causes paranoia. 121 people with paranoid ideation were randomised to receive placebo, THC or THC preceded by a cognitive awareness condition. THC significantly increased paranoia, negative effect (anxiety, worry, depression, negative thoughts about the self) and a range of anomalous experiences, and reduced working memory capacity. The increase in negative effect and anomalous experiences fully accounted for the increase in paranoia. It was definitely demonstrated that the drug triggers paranoid thoughts in vulnerable individuals.

2014 Ortiz-Gomez and others looked at factors associated with depression and suicide attempts in patients undergoing rehabilitation for substance abuse. 57 patients attending a centre for drug abuse treatment were involved in the study - alcohol and marijuana were the drugs studied. 68.4% had current major depression. They concluded that 'Patients with depression who attempted suicide prior to the use of drugs also experienced these conditions during the rehabilitation process. Substance use in the family was a risk factor for both.

2014 Lisdahl K, director of the brain imaging and neuropsychology lab at University of Wiskonsin-Milwaukee, in a presentation to American Psychological Association's 122nd Annual Convention said that: 'Frequent marijuana use (around once/week) can have a significant negative effect on the brains of teenagers and young adults, including cognitive decline, poor attention and memory, and decreased IQ. Abnormalities in the brain's gray matter (assoc with intelligence) have been found in 16 – 19 year olds who increased use over the past year.

2014 Battistella et al looked at the Long-term Effects of Cannabis on Brain Structure. Regular smokers were compared with occasional smokers matched by years of cannabis smoking. Regular cannabis use is associated with reduction of gray matter volume in the medial temporal cortex, temporal pole, para hippocampal gyrus, insula and orbitofrontal cortex. These are areas rich in cannabinoid CB1 receptors and functionally associated with motivational, emotional and affective processing. These changes correlate with the frequency of cannabis use before inclusion in the study. Age of onset also influences the magnitude of these changes. Significant gray matter volume reduction could result either from heavy consumption unrelated to the age of onset or instead from recreational cannabis use initiated at an adolescent age. In contrast, the larger gray matter volume detected in the cerebellum of regular smokers without any correlation with the monthly consumption of cannabis may be related to developmental processes occurring in adolescence (lack of pruning).

2014 Van Gastel and others looked at changes in cannabis use in the general population and psychotic experiences. 705 (18-27 year olds) gave information on their cannabis use and again six months later, then after 5 years. A decrease in cannabis use was associated with a decrease in total psychotic experiences. An increase in use was associated with increased positive symptoms, but not significantly linked with negative and depression symptom scores nor total number of psychotic experiences.

2014 Filbey et al using MRI techniques found that chronic marijuana users have smaller brain volume in the OFC (Orbitofrontal Cortex, a part of the brain commonly associated with addiction), but also increased brain connectivity. 48 adult marijuana users (average 3 times/day) and 62 gender and age matched non-users were studied. The study provides evidence (according to the authors) that chronic marijuana use initiates a complex process that allows neurons to adapt and compensate for smaller gray matter volume. Eventually the structural conductivity (wiring) of the brain starts degrading with prolonged use, but marijuana users continue to display more intense conductivity than healthy non-users. This may help to explain why chronic long-term users seem to be doing 'just fine' despite smaller OFC volumes. Age of first use and duration of use are of vital importance.

2014 Gibbs et al looked at cannabis use and the incidence of manic symptoms and their occurrence in those already diagnosed with pre-existing bipolar disorder mania. A systematic review of the scientific literature were searched, 6 met the inclusion criteria. 2391 individuals had experienced manic symptoms, mean length of follow-up was 3.9 years. An association was found between cannabis use and the exacerbation of manic symptoms in those previously diagnosed with bipolar disorder. Also, a meta-analysis of 2 studies showed that cannabis use is associated with an approximately 3-fold increased risk for the new onset of manic symptoms. Although only a small number of studies was available, they concluded that cannabis use may worsen the occurrence of manic symptoms in those with bipolar disorder, it may also be a causal factor in the incidence of manic symptoms.

2014 Nov Renard et al investigated the log-term consequences of adolescent cannabinoid exposure in adult psychopathology. They concluded that early onset marijuana use has long-lasting consequences on cognition in humans and is associated with a two-fold increase in the risk of developing a psychotic disorder.

2014 Nov Zorrilla and others investigated bipolar disorder and quitting cannabis during manic/mixed episodes. They found that bipolar patients who stop using cannabis during manic/mixed episode have similar clinical and functional outcomes to never users, while continued use is associated with higher risk of recurrence and poorer functioning.

2014 Lorenzetti et al looked at brain changes with chronic heavy cannabis use. Fifteen very heavy smokers of cannabis with minimal psychiatric comorbidity or significant exposure to other substances were compared with 15 age and IQ matched non-cannabis using controls. The heavy users demonstrated smaller hippocampus and amygdala volumes but no alterations in the orbito-frontal and anterior- and paracingulate cortices or the pituitary gland.

2014 Di Forti et al looked at the age of onset of psychosis and the potency of skunk. Patients with a history of cannabis use (daily) presented with their first episode of psychosis at an earlier age than those who had never used. Those who started under 15 had an earlier onset than those who started after 15 years. Those who used high potency cannabis (skunk) every day had the earliest onset compared to never users among all the groups – average of 6 years earlier than that of non-users.

2014 Wilkinson et al found that marijuana may actually worsen PTSD symptoms and increase violent behaviour. 2,276 participants, admitted to specialised Veterans Administration treatment programmes for PTSD between 1991 and 2011 were split into 4 groups - 831 who started taking marijuana (starters), 850 who never used marijuana (never used) 296 who used marijuana at admission and after discharge (continuing use) and 299who stropped using marijuana after treatment. (stoppers).
Those who never used marijuana had significantly lower symptom severity 4 months later than those who continued or started use after treatment. On the other hand, the highest levels of violent behavior were found in the so-called "starters," those who were not using the substance at admission but who started use after discharge.

2014 Fleur et al predicted intimate partner violence by type of substance use disorder. All patients (N = 1799) were screened for IPV perpetration and victimization; almost one third of the sample committed or experienced any IPV in the past year. For males, an alcohol use disorder in combination with
a cannabis and/or cocaine use disorder significantly predicted any IPV (perpetration and/or victimization)
as well as severe IPV perpetration. For females, alcohol and cocaine abuse/dependence predicted both any
IPV(perpetration and/or victimization) and severe IPV perpetration. Results from the present study emphasize the importance of routinely assessing IPV in patients in substance abuse treatment and demonstrate that clinicians should be particularly alert for IPV in patients with specific substance use disorder combinations.

2014 Day et al looked at PME (Prenatal Marijuana Exposure), age of marijuana initiation, and the development of psychotic symptoms in young adults. 763 pregnant women who completed the birth assessment in their fourth prenatal month, were selected for follow-up. Women and their offspring were followed till the offspring were 22 years of age (596 offspring were evaluated). PME and EAOM (Early Age Onset Marijuana) significantly predicted increased rates of PS (Psychotic Symptoms) at 22 years of age, controlling for other significant co-variants. They concluded that PME in addition to EAOM, may also play a role in the association between marijuana use and the development of PS.

2014 Chabrol et al looked at the association between personality disorders traits and problematic cannabis use in adolescents. Participants were 111 high school students. They found that personality disorder traits explained a high part of the variance in problematic cannabis use symptoms. Schizotypal and borderline personality traits were positively associated to problematic cannabis use symptoms after adjustment for anxious and depressive symptoms.

2014 Large et al conducted a meta-analysis of outcomes associated with psychosis and co-morbid substance abuse. Current substance-using patients were significantly younger than non-substance-using patients and more likely to be male. They did not differ in age at onset of psychosis or in level of education. Current substance users had higher rates of positive symptoms and were more likely to have a history of violence. Older studies reported a stronger association between current substance abuse and positive symptoms than those more recently published. Current substance abusers did not differ from non-users on measurements of negative symptoms, depressive symptoms, social function, self-harm or number of hospital admissions. They concluded: Current substance users with psychosis may have more severe positive symptoms than patients never used substances, but this result should be interpreted with caution because of demographic differences between substance users and non substance users.

2014 Valmaggia et al looked at cannabis use and transition to psychosis in people at ultra-high risk. Among current cannabis users, frequent use, early onset use and continued use after clinical presentation were associated with transition to psychosis.

2014 Stone et al looked at cannabis and first episode psychosis: relationship with manic and psychotic symptoms and with age at presentation. They found that the level of cannabis use was associated with a younger age at presentation, manic symptoms and conceptual disorganisation, but not with delusions, hallucinations, negative symptoms or daily functioning. Cannabis users who reduced or stopped their use following contact with services had the greatest improvement in symptoms at one year compared with continued users and non-users. Continued users remained

more symptomatic than non-users at follow-up. Conclusion: Effective interventions for reducing cannabis use may yield significant health benefits for patients with first-episode psychosis.

2014 Radhakrishnan et al reviewed the association of cannabis with psychosis. Abstract: 'Cannabis is the most commonly used illicit drug worldwide, with ~5 million daily users worldwide. Emerging evidence supports a number of associations between cannabis and psychosis/psychotic disorders, including schizophrenia. These associations-based on case-studies, surveys, epidemiological studies, and experimental studies indicate that cannabinoids can produce acute, transient effects; acute, persistent effects; and delayed, persistent effects that recapitulate the psychopathology and psychophysiology seen in schizophrenia. Acute exposure to both cannabis and synthetic cannabinoids (Spice/K2) can produce a full range of transient psychotomimetic symptoms, cognitive deficits, and psychophysiological abnormalities that bear a striking resemblance to symptoms of schizophrenia. In individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. Several factors appear to moderate these associations, including family history, genetic factors, history of childhood abuse, and the age at onset of cannabis use. Exposure to cannabinoids in adolescence confers a higher risk for psychosis outcomes in later life and the risk is dose-related. Individuals with polymorphisms of COMT and AKT1 genes may be at increased risk for psychotic disorders in association with cannabinoids, as are individuals with a family history of psychotic disorders or a history of childhood trauma. The relationship between cannabis and schizophrenia fulfills many but not all of the standard criteria for causality, including temporality, biological gradient, biological plausibility, experimental evidence, consistency, and coherence. At the present time, the evidence indicates that cannabis may be a component cause in the emergence of psychosis, and this warrants serious consideration from the point of view of public health policy'.

2015 Di Forti et al looked at first-epsode psychosis attributable to high-potency cannabis in South London. 410 patients (2005-2011) with first episode psychosis were compared with 370 controls. The risk of individuals having a psychotic disorder showed a roughly 3 times increase in users of skunk-like cannabis compared with those who had never used. Use of skunk-like cannabis every day conferred the highest risk of psychotic disorders compared with the never-users - around 5 times. The population attributable fraction of first episode psychosis for skunk use for our geographical area was 24% probably because of the high prevalence of high potency cannabis by 218 of 410 patients (53%) in the study.

2015 Murray conducted a review of the links between cannabis and psychosis and schizophrenia, 'Appraising the Risks of Reefer Madness'.

2015 May, Estevez et al looked at ADHD and its association with substance use and substance use disorder in young men. 5677 Swiss young men (mean age 20 plus or minus 1.23 years) were studied. Men with ADHD were more likely to report having used nicotine, cannabis and other illicit drugs at some time in their life, but not alcohol. ADHD was positively associated with early initiation of alcohol, nicotine and cannabis use, the risky use of these substances, and the presence of alcohol use disorders, and nicotine and cannabis dependence. Additionally, our analyses revealed that these patterns are also highly associated with ASPD (Anti Social Personality Disorder). After adjusting for this disorder, the association between ADHD and licit and illicit substance use and the presence of SUD (Substance Use Disorders) was reduced, but remained significant.

2015 May, Delforterie et al Looked at the relationship between cannabis involvement and suicidal thoughts and behaviours. All levels of cannabis involvement were related to SI (Suicidal ideation). Cannabis use and endorsing 3 or more cannabis use disorder symptoms were associated with unplanned, but not planned suicide attempts. Associations persisted even after controlling for other psychiatric disorders and substance involvement. Overlapping genetic and environmental factors were responsible for the covariance between cannabis involvement and SI. They concluded that cannabis involvement is associated, albeit modestly, with SI and unplanned suicide attempts. Such attempts are difficult to prevent and their association with cannabis use and cannabis use disorder symptoms requires further study, including in different samples and with additional attention to confounders.

2015 June 6th, Mizrahi et al found that pot can pose a psychosis risk for teens with developing brains. In those that are vulnerable, it doubles the risk. 'They present with hallucinations, seeing things, hearing things, sometimes they will try to self-harm or go after other people'. Genetics, social issues, marijuana strength and frequency of use are among the complex variables with how use starts. Brain development continues till the twenties and cannabis affects the brain's regulator system, the endo-cannabinoid system

which controls things like mood and memory. Psychotic episodes can be short-lived or trigger a long-term illness. Past-year use of cannabis in Ontario is estimated at 23% of grades 7-12, and 40% for those aged 18-29.

2015 Zaman et al studied the co-occurrence of substance-related and other mental health disorders among adolescent cannabis users. We analyzed intake data from 483 adolescents referred for evaluation at an adolescent substance abuse clinic, with information gleaned from the adolescents and their parents or caregivers. Forty-seven percent of our sample met the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) criteria for cannabis dependence and another 32% for cannabis abuse. Among adolescents with cannabis use disorders, the co-occurrence of alcohol and opioid abuse or dependence was high. These individuals also suffered from significant psychiatric comorbidities otherwise. Our results show that cannabis use carries the risk of dependence and also carries with it significant risk of comorbidities, both with respect to other substance use disorders and other psychiatric illness. Given the growing body of research linking cannabis use with addiction and other psychiatric illness, public health efforts ought to center on the potential dangers of cannabis use.

2015 Wetherill and others investigated cannabis, cigarettes, their co-occurring use and differences in gray matter volume. 4 groups were used – cannabis dependents only (Cs), cannabis dependents smoking tobacco (CTs), tobacco dependents only (Ts) and healthy controls (HCs). Compared to HCs, the Cs, Ts and CTS exhibited larger gray matter volume in the left putamen. Cs had larger gray matter volume in the right pre-central gyrus than the HCs. Cs and CTs had smaller gray matter volume in the HCs in the thalamus, and CTs and Ts had smaller cerebellar gray matter volumes than the HCs. This provides evidence that cannabis and tobacco exposure are associated with alterations in brain regions associated with addiction.

2015 Hjorthoj et al assessed the association between mortality and lifetime substance use disorder in patients with schizophrenia, bipolar disorder or unipolar depression. 4,1470 people with schizophrenia, 11,739 with bipolar disorder and 88,270 with depression were studied. They concluded that Mortality in people with mental illness is far higher in people with substance-use disorders than in those without, partularly in people who misuse alcohol and hard drugs.

2015 French et al investigated whether the use of cannabis during early adolescence (by 16) was associated with variations in brain maturation as a function of genetic risk for schizophrenia as assessed with a polygenic risk score. 1,577 participants were studied. They reported a negative association between cannabis use in early adolescence and cortical thickness in male participants with a high polygenic risk score.

2015 Hamilton et al looked at cannabis psychosis and gender. Large data sets over 11 years were used. Data suggests that twice as many males as females use cannabis. This gender ratio is mirrored in rates of psychosis with males outnumbering females by 2:1. But the research team found that there is a significant widening of this ration for cannabis psychosis where males outnumber females by 4:1.

2015Mashhoon et al looked at cortical thinness and volume differences associated with marijuana abuse in emerging adults. Whole brain CT analysis revealed marijuana users had significantly less cortical thickess in their right fusiform gyrus compared to non-users. Thalamic volume was significantly smaller in users compared to non-users and associated with non-planning and overall impulsivity. So cortical thinness and smaller thalamic volume is associated with marijuana abuse. This may interfere with their known roles in regulating visuo-perceptual and object information processing.

2015 Tunbridge et al Looked at the effect of the COMT gene on working memory and psychosis. The study investigated the moderation of the impact of experimentally administered THC by COMT. 78 paticipants, vulnerable to paranoia were used in a double-blind experiment. With respect to cognitive effects, the THC impaired performance in COMT Val/Val but not Met carriers. Psychosis was unaffected by the COMT genotype.

2015 Renard et al looked at long-term structural and functional changes in the prefrontal cortex (PFC) in chronic use by adolescent rats. They found that there were changes in synaptic structure and function in the PFC and that these changes provide key insight to structural functioning and molecular underpinnings of long-term cognitive deficits induced by adolescent cannabinoid exposure. ‘They suggest that cannabinoids may impede the structural maturation on neuronal circuits in the PFC, thus leading to impaired cognitive functioning in adulthood’.

2015 Helle et al investigated cannabis use, schizophrenia and early onset. 1119 Norwegian patients with schizophrenia spectrum disorders were recruited and studied. Patients with substance abuse (627) had about 3 years earlier age at onset than the abstinent group. Only cannabis use was statistically significantly related to earlier age at onset. Gender or family history of psychosis did not influence the results.

2015 Cortes-Briones et al found that cannabis increases the noise in the brain. THC increases random neural activity in the brain (neural noise) of healthy individuals. Half to a single joint produced psychosis-like effects and increased neural noise. There is a dose-dependent and strong positive relationship between these findings, disrupting the brain's normal information processing. The electrical brain activity in 24 people was studied over 3 days.

2015 Rigucci et al investigated the effect of high-potency cannabis on the microstructure of the corpus callosum (crucial part of brain responsible for communication between the two brain hemispheres, composed of white matter fibres, called axons). They found 'the more cannabis you smoke and the higher the potency the worse the damage will be'. They examined the white matter in the brains of 56 people who reported a first episode psychosis at the South London and Maudsley NHS Foundation Trust, and 43 healthy participants from the local area. They also discovered that 'frequent use of high potency cannabis significantly affects the structure of white matter fibres in the brain whether you have psychosis or not'. The worst damage (lesions) was seen in the most posterior part of the corpus callosum.

2016 Laviolette et al looked at the risks of schizophrenia in adolescent rodents. Substantial and persistent behavioural, neuronal and molecular changes that arte identical to neuro-psychiatric conditions such as schizophrenia were observed. They were socially withdrawn, had increased anxiety, cognitive disorganisation and abnormal levels of dopamine – all factors present in clinical populations of schizophrenia. These changes continued into early adulthood, well past the initial exposure. Adults exposed in the same way did not show the same changes.

2016 Morgan et al looked at the AKT1 gene on 442 healthy young cannabis users while intoxicated with their own cannabis and 7 days after when drug free. Around half the population carries this gene. Variation at one locus of the AKT1 gene predicted acute psychotic response to cannabis along with dependence on the drug and baseline schizotypal symptoms. Working memory following cannabis acutely was worse in females. These are the first findings to demonstrate that AKT1 mediates the acute response to cannabis in otherwise healthy individuals and implicate the AKT1 pathway as a possible target for prevention and treatment of cannabis psychosis.

2016 Blanco et al looked at cannabis use and the risk of psychiatric disorders. Respondents in the US aged 18 or over, mean age 45.1 years, were interviewed 3 years apart. Cannabis use in 'wave 1' (2001-2) reported by 1279 respondents, was significantly associated with substance use disorders in 'wave 2' (2004-5). Any substance use disorder OR (Odds Ratio) 6.2, any alcohol use disorder OR 2.7, any cannabis use disorder OR 9.5, any other drug use disorder OR 2.6 and nicotine dependence OR 1.7. No mood disorder OR1.1 or anxiety disorder OR 0.9. Cannabis use is associated with an increase for several substance use disorders.

2016 Patel et al looked at the association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis. Anonymised electronic mental health record data from The South London and Maudsley NHS Foundation Trust was used. They found **c**annabis use present in 46.3% of the sample at first presentation and was particularly common in patients who were 16–25, male and single. It was associated with increased frequency of hospital admission, increased likelihood of compulsory admission, and greater number of days spent in hospital. The number of unique antipsychotics prescribed, mediated increased frequency of hospital admission, increased likelihood of compulsory admission, and greater number of days spent in hospital. **Conclusions** Cannabis use in patients with FEP was associated with an increased likelihood of hospital admission. This was linked to the prescription of several different antipsychotic drugs, indicating clinical judgement of antipsychotic treatment failure. Together, this suggests that cannabis use might be associated with worse clinical outcomes in psychosis by contributing towards failure of antipsychotic treatment.

2016 Schoeler et al looked at continuing use and discontinuingof cannabis in patients with psychosis. Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

2016 Kelley et al looked at marijuana use in the immediate 5-year pre-mormid period and its association with increased onset of schizophrenia and related psychotic disorders. They concluded 'These data provide evidence of a clear temporal relationship between escalations in use in the five years pre-onset and an

increased rate of onset, demonstrate that the strength of the association is similar pre- and post-onset of prodromal symptoms, and determine that early adult use may be just as important as adolescent use in these associations'.

2016 Bechtold et al looked at marijuana use in adolescence and the risk of psychotic symptoms. 1009 males from first grade through 18 years. Study participants were recruited in first and seventh grades. Marijuana use, subclinical psychotic symptoms and time-varying co-variants e.g. other substance use, internalizing/externalising problems were determined from ages 13 to 18 via self-reports. For each adolescent year boys engaged in regular marijuana use, their projected level of subsequent sumclinical psychotic symptoms increased by 21% and projected risk for subclinical paranoia or hallucinations increased by 133% and 92% respectively. This effect persisted through 1 year of abstinence.

2016 Filbey et al looked at long-term marijuana use and alteration in the brain's reward circuit. 59 adult marijuana users (average 12 years of use) and 79 non-users were involved. Reserchers found that long-term marijuana users had more brain activity in the mesocorticolimbic reward system when presented with cannabis cues than with natural reward cues. 'This study shows that marijuana disturbs the natural reward circuitry of the brain , making marijuana highly salient to those who already use it heavily. In essence, these brain alterations could be a marker of transition from recreational marijuana use to problematic use', sad Dr Filbey. Cannabis cues included bongs, pipes, joints or blunts as compared with self-selected preferred fruit, banana, apple, orange or grapes.

2016 Xie et al looked at associations between co-morbid cigarette, alcohol and marijuana use and psychopathology. A random community based sample of 973individuals, primarily white from upstate New York, with a mean age of 36.6 were studied. They found that in this large community based sample, long-term simultaneous use of alcohol, cigarettes and marijuana was associated with psychiatric disorders in adulthood, such as ASPD (Anti-social Personality Disorder, MDE (Major Depressive Episode), and GAD. Generalised Anxiety Disorder. Social and environmental factors were not examined and it may be possible that precursors to adult psychopathology such as childhood conduct disorder may precede long-term substance abuse.

2016 Martz et al found that marijuana use dampens brain response to reward over time. Measurable changes were found in the brain reward system with marijuana use even when other factors like alcohol and tobacco use were taken into account. 108 people in their early 20s, taking part in a larger study on substance abuse had brain scans at 3 points over 4 years (75% men, almost all white). In the moment of anticipating a reward (e.g. may win money) the nucleus accumbens (part of the reward system) pumps out dopamine (pleasure neurotransmitter), the greater the anticipation the more dopamine is produced. However the more marijuana used, the smaller the response over time. This suggests that long-term marijuana use dampens the emotional response of a person – anhedonia. These brain changes may increase the risk of continued drug use and addiction.

2016 Mandelbaum et al looked at the adverse effects of marijuana on the brain. The legalisation push for medical and recreational use of marijuana is spreading. It is critical that societal passions not obscure objective assessments of its short and long-term adverse effects especially in relation to its onset of use and chronicity of exposure. 'This critical review focuses on evidence-based research designed to assess both therapeutic benefits and harmful effects of cannabis exposure, and is combined with an illustration of the neuropathological findings in a fatal case of cannabis-induced psychosis. The literature and reported case provide strong evidence that chronic cannabis abuse causes cognitive impairment and damages the brain, particularly white matter, where cannabinoid 1 receptors abound. Contrary to popular perception, there is little objective data supporting preferential use of cannabis over conventional therapy for restoration of central nervous system structure and function in disease states such as multiple sclerosis, epilepsy, or schizophrenia. Additional research is needed to determine if sub-sets of individuals with various neurological and psychiatric diseases derive therapeutic benefits from cannabis'.

2016 Carey et al Looked at genetics and links with mental illness. "Our research shows that if someone is genetically predisposed towards having mental illness, they are also prone to use licit and illicit substances and develop problematic usage patterns," says Caitlin E. Carey, "This is important because if a mental illness, like depression, runs in your family, you are presumed at risk of that disorder. But we find that having a genetic predisposition to mental illness also places that person at risk for substance use and addiction." "Previous research on the genetic overlap of mental illness and drug use has been limited to family studies. This has made it difficult to examine some of the less common disorders," says Carey. "For example, it's hard to find families where some members have schizophrenia and others abuse cocaine. With

this method we were able to compare people with various levels of substance involvement to determine whether they were also at relatively higher genetic risk for psychiatric disorders."

As well as finding an overall genetic relationship between mental health and substance involvement, the study revealed links between specific mental illnesses and drugs. "For example, we found that genetic risk for both schizophrenia and depression are associated with cannabis and cocaine involvement."

2016 Nielsen et al looked at abuse of alcohol and other illicit drugs and schizophrenia risk. Danish records of 3.1 million people's medical records were investigated. The y found the increased risk of schizophrenia from cannabis (skunk) use was 5.2 times, alcohol 3.4, hallucinogenic drugs 1.9, sedatives 1.7, amphetamines 1.24. and other substances 2.8 times. In a second study (Hjorthoj et al), they found that pregnant cannabis-using women had children 6 times more likely to be schizophrenic. For paternal cannabis use there was a 5.5 times increase risk of schizophrenia in the child before/after birth.

2016 Mok et al looked at parental psychiatric disease and risks of attempted suicide and violent criminal offending in offspring. All persons born in Denmark 1967 – 1997 were followed from their 15th birthday till occurrence of adverse outcome or December 31st 2012 whichever came first.

'1 743 525 cohort members (48.7% female) Risks for offspring suicide attempt and violent offending were elevated across virtually the full spectrum of parental psychiatric disease. Incidence rate ratios were the most elevated for parental diagnoses of antisocial personality disorder (suicide attempt, risk 3.96 times; violent offending, 3.62 times; and cannabis misuse (suicide attempt, 3.57 times risk; violent offending, 4.05; and for parental suicide attempt (suicide attempt, 3.42;; violent offending, 3.31 times. Parental mood disorders (and bipolar disorder in particular) conferred more modest risk increases. A history of mental illness or suicide attempt in both parents was associated with double the risks compared with having just 1 affected parent. Associations between parental psychiatric disease and offspring violent offending were stronger for female than for male offspring, whereas little sex difference in risk was found for offspring suicide attempt'. Early interventions to tackle parental mental disorders may be beneficial to both parents and children.

2016 Nesvag et al investigated cannabis use as a possible cause of psychosis. The risk of developing psychosis is more than tripled for those who abuse cannabis according to results from a new twin study at the NIPH (Norwegian Institute of Public Health). The researchers tested both the hypotheses that cannabis use causes psychotic symptoms and that psychotic symptoms lead to cannabis abuse. They found that the twin with symptoms of cannabis abuse had a 3.5 times higher risk of developing symptoms of psychosis compared with the twin with no cannabis abuse. This is also the case in the general population. The other hypothesis was less suited to the data.

2016 Amen et al found abnormally low blood flow in the brain of marijuana users. Abnormally low blood pressure occurred in almost every area of the brain in nearly 1,000 marijuana users compared to healthy controls. The hippocampus, the brain's key learning and memory centre, had the lowest blood flow in marijuana users suggesting higher vulnerability for altzheimer's disease. 28,268 patients were monitored.

2016 Marconi et al conducted a meta-analysis of the aassociation between the level of cannabis use and risk of schizophrenia. Abstract:Cannabis use has been reported to induce long-lasting psychotic disorders and a dose-response relationship has been observed. We performed a systematic review of studies that investigate the association between the degree of cannabis consumption and psychosis and a meta-analysis to quantify the magnitude of effect. Published studies were identified through search of electronic databases, supplemented by manual searches of bibliographies. Studies were considered if they provided data on cannabis consumption prior to the onset of psychosis using a dose criterion (frequency/amount used) and reported psychosis-related outcomes. We performed random effects meta-analysis of individual data points generated with a simulation method from the summary data of the original studies. From 571 references, 18 studies fulfilled inclusion criteria for the systematic review and 10 were inserted in the meta-analysis, enrolling a total of 66 816 individuals. Higher levels of cannabis use were associated with increased risk for psychosis in all the included studies. A logistic regression model gave an OR of 3.90 (95% CI 2.84 to 5.34) for the risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to the nonusers. Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis. Although a causal link cannot be unequivocally established, there is sufficient evidence to justify harm reduction prevention programs.

2017 Vaucher et al looked at cannabis use and the risk of schizophrenia. Using a genetic approach, we took 10 independent genetic variants previously identified to associate with cannabis use in 32 330 individuals

to determine the nature of the association between cannabis use and risk of schizophrenia. Genetic variants were employed as instruments to recapitulate a randomized controlled trial involving two groups (cannabis users vs nonusers) to estimate the causal effect of cannabis use on risk of schizophrenia in 34 241 cases and 45 604 controls from predominantly European descent. Genetically-derived estimates were compared with a meta-analysis of observational studies reporting ever use of cannabis and risk of schizophrenia or related disorders. Based on the genetic approach, use of cannabis was associated with increased risk of schizophrenia (odds ratio (OR) of schizophrenia for users vs nonusers of cannabis: 1.37. The corresponding estimate from observational analysis was 1.43. The genetic markers did not show evidence of pleiotropic effects and accounting for tobacco exposure did not alter the association (OR of schizophrenia for users vs nonusers of cannabis, adjusted for ever vs never smoker: 1.41. This adds to the substantial evidence base that has previously identified cannabis use to associate with increased risk of schizophrenia, by suggesting that the relationship is causal. Such robust evidence may inform public health messages about cannabis use, especially regarding its potential mental health consequences.

2017 Bianca et al looked at cannabis use and the risk for substance use disorders and mood or anxiety disorders using longitudinal data. A nationally representative sample of US adults, 34,653, aged 18 or older, was interviewed in waves 3 years apart (2001-2002 to 2004-2005). Cannabis use was reported from1279 respondents and was significantly associated with substance disorders in wave2. |Any substance disorder Odds Ratio 6.2, alcohol use disorder 2.7, any cannabis use disorder 9.2, any other drug use disorder 2.6 and nicotine dependence 1.7, but not any mood or anxiety disorder.

2017 Dorard et al investigated a possible link between alexithymia (inability to express emotions or understand emotions in others) and cannabis use disorder (CUD).
'120 young patients (95 males - mean age 17.9years with a cannabis dependence or abuse, seeking treatment in an addiction unit, and 110 healthy control subjects (77 males - mean age 18.2years, participated in the study. They completed a battery of self-reports measuring alexithymia , depression and state and trait anxiety. They found that 35.3% of cannabis users were alexithymic, and logistic regression analysis showed that the alexithymic components of difficulties identifying and describing feelings combined with trait anxiety predicted group membership'.

2017 Chye et al examined cannabis-related hippocampal volumetric abnormalities specific to subregions in dependent users. 'The objective of the study is to investigate gray matter alteration in each of the hippocampal subregions (presubiculum, subiculum, cornu ammonis (CA) subfields CA1-4, and dentate gyrus (DG)) as associated with cannabis use and dependence. A total of 35 healthy controls (HC), 22 non-dependent (CB-nondep), and 39 dependent (CB-dep) cannabis users were recruited. We investigated group differences in hippocampal subregion volumes between HC, CB-nondep, and CB-dep users. We further explored the association between CB use variables (age of onset of regular use, monthly use, lifetime use) and hippocampal subregions in CB-nondep and CB-dep users separately. The CA1, CA2/3, CA4/DG, as well as total hippocampal gray matter were reduced in volume in CB-dep but not in CB-nondep users, relative to HC. The right CA2/3 and CA4/DG volumes were also negatively associated with lifetime cannabis use in CB-dep users. Our results suggest a regionally and dependence-specific influence of cannabis use on the hippocampus. Hippocampal alteration in cannabis users was specific to the CA and DG regions and confined to dependent users'.

2017 Chye et al looked at orbitofrontal and caudate volumes in cannabis users. 'The objective of this study was to investigate the association between CB use and dependence, and the volumes of brain regions critically involved in goal-directed learning and behaviour-the orbitofrontal cortex (OFC) and caudate. In the largest multi-site structural imaging study of CB users vs healthy controls (HC), 140 CB users and 121 HC were recruited from four research sites. Group differences in OFC and caudate volumes were investigated between HC and CB users and between 70 dependent (CB-dep) and 50 non-dependent (CB-nondep) users. The relationship between quantity of CB use and age of onset of use and caudate and OFC volumes was explored. CB users (consisting of CB-dep and CB-nondep) did not significantly differ from HC in OFC or caudate volume. CB-dep compared to CB-nondep users exhibited significantly smaller volume in the medial and the lateral OFC. Lateral OFC volume was particularly smaller in CB-dep females, and reduced volume in the CB-dep group was associated with higher monthly cannabis dosage. They concluded that smaller medial OFC volume may be driven by CB dependence-related mechanisms, while smaller lateral OFC volume may be due to ongoing exposure to cannabinoid compounds. The results highlight a distinction between cannabis use and dependence and warrant examination of gender-specific effects in studies of CB dependence'.

2017 Schoeler et al looked at poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis. In a prospective analysis of data acquired from four

different adult inpatient and outpatient units of the South London and Maudsley Mental Health National Health Service Foundation Trust in London, UK, 245 patients were followed up for 2 years from the onset of first-episode psychosis. Continued cannabis use predicted poor outcome, including risk of relapse, number of relapses, length of relapse, and care intensity at follow-up. Between 20% and 36% of the adverse effects of continued cannabis use on outcome in psychosis might be mediated through the effects of cannabis use on medication adherence. Interventions directed at medication adherence could partly help mitigate the harm from cannabis use in psychosis.

2017 Bourque et al investigated marijuana and the vulnerability to psychosis. Progressing from occasional use to weekly or daily use of marijuana can increase the risk to an adolescent of having recurrent psychotic experiences by 159%. They discovered that an increase in symptoms of depression such as low mood and negative thoughts could explain this relationship. Approximately 4000 adolescents of 13 years of age from 31 Montreal schools. Every year from grades 7 to 11 they filled in computerized questionnaires.

2017 Ecker et al Looked at cannabis-related problems and social anxiety. 'Cannabis is the most commonly used illicit drug in the US, and is associated with a range of psychological, social, and physical health-related problems. Individuals who endorse elevated levels of social anxiety are especially at risk for experiencing cannabis-related problems, including cannabis use disorder, despite not using cannabis more often than those with more normative social anxiety. Identification of mechanisms that underlie the relationship between social anxiety and cannabis-related problems may inform treatment and prevention efforts. Post-event processing (PEP, i.e., cognitively reviewing past social interactions/performances) is a social anxiety-related phenomenon that may be one such mechanism. The current study sought to test PEP as a mediator of the relationship between social anxiety and cannabis-related problems, adjusting for cannabis use frequency.Cannabis-using (past 3-month) undergraduate students recruited in 2015 (N = 244; 76.2% female; 74.2% Non-Hispanic Caucasian) completed an online survey of cannabis use, cannabis-related problems, social anxiety, and PEP. Bootstrap estimate of the indirect effect of social anxiety through PEP was significant, suggesting PEP is a mediator of the social anxiety-cannabis-related problems relationship. Conclusions/Importance: Treatment and prevention efforts may benefit from targeting PEP among individuals with elevated social anxiety and cannabis-related problems'.

2017 Malyshevskaya et al Found that natural THC and Spice could induce seizures. 'Natural cannabinoids and their synthetic substitutes are the most widely used recreational drugs. Numerous clinical cases describe acute toxic symptoms and neurological consequences following inhalation of the mixture of synthetic cannabinoids known as "Spice." Here we report that an intraperitoneal administration of the natural cannabinoid Δ9-tetrahydrocannabinol (10 mg/kg), one of the main constituent of marijuana, or the synthetic cannabinoid JWH-018 (2.5 mg/kg) triggered electrographic seizures in mice, recorded by electroencephalography and videography. Administration of JWH-018 (1.5, 2.5 and 5 mg/kg) increased seizure spikes dose-dependently. Pretreatment of mice with AM-251 (5 mg/kg), a cannabinoid receptor 1-selective antagonist, completely prevented cannabinoid-induced seizures. These data imply that abuse of cannabinoids can be dangerous and represents an emerging public health threat. Additionally, our data strongly suggest that AM-251 could be used as a crucial prophylactic therapy for cannabinoid-induced seizures or similar life-threatening conditions'.

2017 Guttmannova et al assessed the association between regular marijuana use and adult mental health outcomes. The present study is a prospective examination of the relationship between regular marijuana use from adolescence through young adulthood and mental health outcomes at age 33.Data came from a gender-balanced, ethnically diverse longitudinal panel of 808 participants from Seattle, Washington. Outcomes included symptom counts for six mental health disorders. Regular marijuana use was tracked during adolescence and young adulthood. Regression analyses controlled for demographics and early environment, behaviors, and individual risk factors.Nonusers of marijuana reported fewer symptoms of alcohol use disorder, nicotine dependence, and generalized anxiety disorder than any category of marijuana users. More persistent regular marijuana use in young adulthood was positively related to more symptoms of cannabis use disorder, alcohol use disorder, and nicotine dependence at age 33.Findings highlight the importance of avoiding regular marijuana use, especially chronic use in young adulthood. Comprehensive prevention and intervention efforts focusing on marijuana and other substance use might be particularly important in the context of recent legalization of recreational marijuana use in Washington and other U.S. states.

2017 Frissen et al examined Abstract: 'whether cannabis use, childhood trauma and urban upbringing are associated with total gray matter volume (GMV) in individuals with (risk for) psychotic disorder and whether this is sex-specific. T1-weighted MRI scans were acquired from 89 patients with a psychotic disorder, 95 healthy siblings of patients with psychotic disorder and 87 controls. Multilevel random regression analyses were used to examine main effects and interactions between group, sex and

environmental factors in models of GMV. The three-way interaction between group, sex and cannabis ($\chi2$ =12.43, p<0.01), as well as developmental urbanicity ($\chi2$ = 6.29, p = 0.01) were significant, indicating that cannabis use and developmental urbanicity were associated with lower GMV in the male patient group (cannabis: B= -32.54, p < 0.01; developmental urbanicity: B= -10.23, p=0.03). For childhood trauma, the two-way interaction with group was significant ($\chi2$ = 5.74, p = 0.02), indicating that childhood trauma was associated with reduced GMV in the patient group (B=-9.79, p=0.01). The findings suggest that reduction of GMV in psychotic disorder may be the outcome of differential sensitivity to environmental risks, particularly in male patients'.

2017 Foster et al looked at psychosocial functioning among regular cannabis users with and without cannabis use disorder. 'In the United States, cannabis accessibility has continued to rise as the perception of its harmfulness has decreased. Only about 30% of regular cannabis users develop cannabis use disorder (CUD), but it is unclear if individuals who use cannabis regularly without ever developing CUD experience notable psychosocial impairment across the lifespan. Therefore, psychosocial functioning was compared across regular cannabis users with or without CUD and a non-user control group during adolescence (age 17; early risk) and young adulthood (ages 18-25; peak CUD prevalence). Weekly cannabis users with CUD (n = 311), weekly users without CUD (n = 111), and non-users (n = 996) were identified in the Minnesota Twin Family Study. Groups were compared on alcohol and illicit drug use, psychiatric problems, personality, and social functioning at age 17 and from ages 18 to 25. Self-reported cannabis use and problem use were independently verified using co-twin informant report. In both adolescence and young adulthood, non-CUD users reported significantly higher levels of substance use problems and externalizing behaviors than non-users, but lower levels than CUD users. High agreement between self- and co-twin informant reports confirmed the validity of self-reported cannabis use problems. Even in the absence of CUD, regular cannabis use was associated with psychosocial impairment in adolescence and young adulthood. However, regular users with CUD endorsed especially high psychiatric co-morbidity and psychosocial impairment.

2017 Kejser-Starzer et al looked at the rates of conversion to schizophrenia and bipolar disorder following substance-induced psychosis. All patient information was extracted from the Danish Civil Registration System and the Psychiatric Central Research Register. The study population included all persons who received a diagnosis of substance-induced psychosis between 1994 and 2014 (N=6,788); patients were followed until first occurrence of schizophrenia or bipolar disorder or until death, emigration, or August 2014. Overall, 32.2% of patients with a substance-induced psychosis converted to either bipolar or schizophrenia-spectrum disorders. The highest conversion rate was found for cannabis-induced psychosis, with 47.4% converting to either schizophrenia or bipolar disorder. Young age was associated with a higher risk of converting to schizophrenia. Self-harm after a substance-induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder. Half the cases of conversion to schizophrenia occurred within 3.1 years after a substance-induced psychosis, and half the cases of conversion to bipolar disorder occurred within 4.4 years.

2017 Marwaha et al looked at cannabis use and hypomania in young people. Abstract: Cannabis use in young people is common and associated with psychiatric disorders. However, the prospective link between cannabis use and bipolar disorder symptoms has rarely been investigated. The study hypothesis was that adolescent cannabis use is associated with hypomania in early adulthood via several potential etiological pathways. Data were used from the Avon Longitudinal Study of Parents and Children, a UK birth cohort study. The prospective link between cannabis use at age 17 and hypomania at age 22‐23 years was tested using regression analysis, adjusted for gender, early environmental risk factors, alcohol and drug use, and depression and psychotic symptoms at age 18 years. Path analysis examined direct and indirect effects of the link and whether gender, childhood family adversity, or childhood abuse are associated with hypomania via an increased risk of cannabis use. Data were available on 3370 participants. Cannabis use at least 2‐3 times weekly was associated with later hypomania (OR = 2.21) after adjustment. There was a dose‐response relationship (any use vs weekly). Cannabis use mediated the association of both childhood sexual abuse and hypomania, and male gender and hypomania. The cannabis use-hypomania link was not mediated by depression or psychotic symptoms. Adolescent cannabis use may be an independent risk factor for future hypomania, and the nature of the association suggests a potential causal link. Cannabis use mediates the link between childhood abuse and future hypomania.

2018 Manza et al looked at heavy cannabis use and altertion of the activity of brain regions linked to negative emotions. Abstract: Cannabis abuse has been associated with psychopathology, including negative emotionality and a higher risk of psychosis, particularly with early age of initiation. However, the mechanisms underlying this association are poorly understood. Because aberrant dopamine (DA) signaling

is implicated in cannabis-associated psychopathology, we hypothesized that regular cannabis abuse (CA) would be associated with altered resting functional connectivity in dopamine midbrain-striatal circuits. We examined resting brain activity of subcortical regions in 441 young adults from the Human Connectome Project, including 30 CA meeting DSM criteria for dependence, and 30 controls matched on age, sex, education, BMI, anxiety, depression, and alcohol/tobacco usage. Across all subjects, local functional connectivity density (lFCD) hubs in subcortical regions were most prominent in ventral striatum, hippocampus, amygdala, dorsal midbrain, and the posterior-ventral brainstem. As hypothesized, CA showed markedly increased lFCD relative to controls in ventral striatum (where nucleus accumbens is located) and midbrain (where substantia nigra/ventral tegmental nuclei are located) but also in brainstem and lateral thalamus. These effects were observed in the absence of significant differences in subcortical volumes, and were most pronounced in the individuals who began cannabis use earliest in life and who reported high levels of negative emotionality.Together, these findings suggest that chronic cannabis abuse is associated with changes in resting brain function, particularly in dopaminergic nuclei implicated in psychosis but that are also critical for habit formation and reward processing. These results shed light on neurobiological differences that may be relevant to psychopathology associated with cannabis use.

2018 Mustonen et al looked at adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. The sample (*n* = 6534) was composed of the prospective general population-based Northern Finland Birth Cohort of 1986. Information on prodromal symptoms of psychosis and cannabis use was collected using questionnaires at age 15–16 years. Participants were followed up for ICD-10 psychotic disorders until age 30 years using nationwide registers. The risk of psychosis was elevated in individuals who had tried cannabis five times or more (hazard ratio, (HR) = 6.5, 95% CI 3.0–13.9). The association remained statistically significant even when adjusted for prodromal symptoms, other substance use and parental psychosis (HR = 3.0, 95% CI 1.1–8.0). Conclusion:Adolescent cannabis use is associated with increased risk of psychosis even after adjustment for baseline prodromal symptoms, parental psychosis and other substance use.

2018 Renard et al studied the effects of adolescent THC exposure on the prefrontal GABAergic system: Implications for schizophrenia-related psychopathy. Abstract: Marijuana is the most commonly used drug of abuse among adolescents. Considerable clinical evidence supports the hypothesis that adolescent neurodevelopmental exposure to high levels of the principal psychoactive component in marijuana, -delta-9-tetrahydrocanabinol (THC), is associated with a high risk of developing psychiatric diseases, such as schizophrenia later in life. This marijuana-associated risk is believed to be related to increasing levels of THC found within commonly used marijuana strains. Adolescence is a highly vulnerable period for the development of the brain, where the inhibitory GABAergic system plays a pivotal role in the maturation of regulatory control mechanisms in the central nervous system (CNS). Specifically, adolescent neurodevelopment represents a critical period wherein regulatory connectivity between higher-order cortical regions and sub-cortical emotional processing circuits such as the mesolimbic dopamine (DA) system is established. Emerging preclinical evidence demonstrates that adolescent exposure to THC selectively targets schizophrenia-related molecular and neuropharmacological signaling pathways in both cortical and sub-cortical regions, including the prefrontal cortex (PFC) and mesolimbic DA pathway, comprising the ventral tegmental area (VTA) and nucleus accumbens (NAc). Prefrontal cortical GABAergic hypofunction is a key feature of schizophrenia-like neuropsychopathology. This GABAergic hypofunction may lead to the loss of control of the PFC to regulate proper sub-cortical DA neurotransmission, thereby leading to schizophrenia-like symptoms. This review summarizes preclinical evidence demonstrating that reduced prefrontal cortical GABAergic neurotransmission has a critical role in the sub-cortical DAergic dysregulation and schizophrenia-like behaviors observed following adolescent THC exposure.

2018 Chye et al looked at alteration to the hippocampal volume and shape confined to cannabis dependence. Cannabis use is highly prevalent and often considered to be relatively harmless. Nonetheless, a subset of regular cannabis users may develop dependence, experiencing poorer quality of life and greater mental health problems relative to non-dependent users. The neuroanatomy characterizing cannabis use versus dependence is poorly understood. We aimed to delineate the contributing role of cannabis use and dependence on morphology of the hippocampus, one of the most consistently altered brain regions in cannabis users, in a large multi-site dataset aggregated across four research sites. We compared hippocampal volume and vertex-level hippocampal shape differences (1) between 121 non-using controls and 140 cannabis users; (2) between 106 controls, 50 non-dependent users and 70 dependent users; and (3) between a subset of 41 controls, 41 non-dependent users and 41 dependent users, matched on sample characteristics and cannabis use pattern (onset age and dosage). Cannabis users did not differ from controls in hippocampal volume or shape. However, cannabis-dependent users had significantly smaller right and

left hippocampi relative to controls and non-dependent users, irrespective of cannabis dosage. Shape analysis indicated localized deflations in the superior-medial body of the hippocampus. Our findings support neuroscientific theories postulating dependence-specific neuroadaptations in cannabis users. Future efforts should uncover the neurobiological risk and liabilities separating dependent and non-dependent use of cannabis.

2018 Leadbeater et al looked at the age-varying effects of cannabis use frequency and disorder on symptoms of psychosis, depression and anxiety in adolescents and adults. Abstract: Adolescent data(V-HYS; N=662) were collected from a randomly recruited sample of adolescents in Victoria, British Columbia, Canada over a 10-year period(2003-2013). Adult cross-sectional data (NESARC-III; N=36,309) were collected from a representative sample from the US(2012-2013). MEASUREMENTS: Mental health symptoms were assessed using self-report measures of diagnostic symptoms. CU was based on frequency of past-year use. Past-year CUD was based on DSM-5 criteria. For youth in the V-HYS, CU was associated with psychotic symptoms following age 22(b=.13, 95%CI =[.002, .25]), with depressive symptoms from ages 16-19 and following age 25(b=.17, 95%CI =[.003, .34]), but not with anxiety symptoms. CUD was associated with psychotic symptoms following age 23(b=.51, 95%CI=[.01, 1.01]), depressive symptoms at ages 19-20 and following age 25(b=.71, 95%CI=[.001, 1.42]), and anxiety symptoms ages 26-27 only. For adults in the NESARC-III, CU was associated with mental health symptoms at most ages(e.g., psychotic symptoms; age 18: b=.22, 95%CI=[.10, .33] to age 65: b=.36, 95%CI=[.16, .56]). CUD was associated with all mental health symptoms across most ages(e.g., depressive symptoms; age 18: b=.96, 95%CI=[.19, 1.73] to age 61: b=1.11, 95%CI=[.01, 2.21]). Interactions with sex show stronger associations for females than males in young adulthood(e.g. , V-HYS: CUD by sex interaction on psychotic symptoms significant after age 26; b=1.12, 95%CI=[.02, 2.21]). Findings were not moderated by early onset CU. Significant associations between CU and CUD and psychotic and depressive symptoms in late adolescence and young adulthood extend across adulthood and include anxiety.

2018 Windle et al looked at Age sensitive associations of adolescent substance use with amygdalar, ventral striatum, and frontal volumes in young adulthood. This study evaluated an age sensitive model of substance use across adolescence to determine if substance use was associated with smaller volumes for an earlier developing brain region, the amygdala, a later developing region, the inferior frontal gyrus, and the ventral striatum. Participants (N = 110) were African American young adults who were members of a longitudinal cohort across childhood and adolescence. Measures of substance use were collected across early (ages 12-15 yrs.), middle (ages 16-18 yrs.), and later (ages 19-21 yrs.) adolescence; then, at age 25, a representative subset of the sample completed magnetic resonance imaging (MRI) that assessed regional brain volumes. Higher levels of substance use during early adolescence, but not middle or later adolescence, were significantly associated with smaller amygdalar volume in young adulthood. Higher levels of substance use during middle adolescence, but not early or later adolescence, were significantly associated with smaller pars opercularis volume. Substance use was not associated with the pars triangularis or ventral striatum. These findings support age sensitive associations between substance use and smaller gray matter volumes at age 25 and are consistent with literature supporting the differential nature of substance use and brain maturation across adolescence and into young adulthood.2019 Saravia et al investigated concomitant THC and stress adolescent exposure induces fear extinction and related neurobiological changes in adulthood. Abstract: Δ9-tetrahydrocannabinol (THC) consumption during adolescence is reported to be a risk factor for the appearance of psychiatric disorders later in life. The interaction between genetic or environmental events and cannabinoid exposure in the adolescent period can also contribute to exacerbate behavioural deficits in adulthood. Here we investigate the effects of THC treatment as well as the consequences of concomitant THC and stress exposure during adolescence in the extinction of fear memory in adult mice. Adolescent mice treated with THC and exposed to stress exhibit impaired cued fear extinction in adulthood. However, no effect was observed in animals exposed to these two factors separately. Notably, resistance to fear extinction was associated with decreased neuronal activity in the basolateral amygdala (BLA) and the infralimbic prefrontal cortex, suggesting a long-term dysregulation of the fear circuit. These changes in neuronal activation were paralleled with structural plasticity alterations. Indeed, an increase of immature dendritic spines in pyramidal neurons of the BLA was revealed in mice simultaneously exposed to THC and stress. Corticosterone levels were also enhanced after the cued fear conditioning session in the same experimental group. These results show that an interaction between cannabis exposure and stress during adolescence may lead to long-term anxiety disorders characterized by the presence of pathological fear.

2019 Orr et al Abstract: Rates of cannabis use among adolescents are high, and are increasing concurrent with changes in the legal status of marijuana and societal attitudes regarding its use. Recreational cannabis use is understudied, especially in the adolescent period when neural maturation may make users particularly vulnerable to the effects of Δ-9-tetrahydrocannabinol (THC) on brain structure. In the current

study, we used voxel-based morphometry to compare grey matter volume (GMV) in 46 fourteen year old human adolescents (males and females) with just one or two instances of cannabis use and carefully matched THC-naïve controls. We identified extensive regions in the bilateral medial temporal lobes as well as the bilateral posterior cingulate, lingual gyri, and cerebellum that showed greater GMV in the cannabis users. Analysis of longitudinal data confirmed that GMV differences were unlikely to precede cannabis use. GMV in the temporal regions was associated with contemporaneous performance on the Perceptual Reasoning Index and with future generalized anxiety symptoms in the cannabis users. The distribution of GMV effects mapped onto biomarkers of the endogenous cannabinoid system providing insight into possible mechanisms for these effects.Significance StatementAlmost 35% of American 10th graders have reported using cannabis and existing research suggests that initiation of cannabis use in adolescence is associated with long-term neurocognitive effects. We understand very little about the earliest effects of cannabis use, however, as most research is conducted in adults with a heavy pattern of lifetime use. This study presents evidence suggesting structural brain and cognitive effects of just one or two instances of cannabis use in adolescence. Converging evidence suggests a role for the endocannabinoid system in these effects. This research is particularly timely as the legal status of cannabis is changing in many jurisdictions and the perceived risk by youth associated with smoking cannabis has declined in recent years.

2019 Di Forti et al looked at the contribution of cannabis use to variation in the incidence of psychotic disorder across Europe.

Summary:**Background** Cannabis use is associated with increased risk of later psychotic disorder but whether it affects incidence of the disorder remains unclear. We aimed to identify patterns of cannabis use with the strongest effect on odds of psychotic disorder across Europe and explore whether differences in such patterns contribute to variations in the incidence rates of psychotic disorder. **Methods** We included patients aged 18–64 years who presented to psychiatric services in 11 sites across Europe and Brazil with first-episode psychosis and recruited controls representative of the local populations. We applied adjusted logistic regression models to the data to estimate which patterns of cannabis use carried the highest odds for psychotic disorder. Using Europe-wide and national data on the expected concentration of Δ^9-tetrahydrocannabinol (THC) in the different types of cannabis available across the sites, we divided the types of cannabis used by participants into two categories: low potency (THC low potency (THC <10%) and high potency (THC =/> 10%). Assuming causality, we calculated the population attributable fractions (PAFs) for the patterns of cannabis use associated with the highest odds of psychosis and the correlation between such patterns and the incidence rates for psychotic disorder across the study sites. **Findings** Between May 1, 2010, and April 1, 2015, we obtained data from 901 patients with first-episode psychosis across 11 sites and 1237 population controls from those same sites. Daily cannabis use was associated with increased odds of psychotic disorder compared with never users (adjusted odds ratio [OR] 3·2, 95% CI 2·2–4·1), increasing to nearly five-times increased odds for daily use of high-potency types of cannabis (4·8, 2·5–6·3). The PAFs calculated indicated that if high-potency cannabis were no longer available, 12·2% (95% CI 3·0–16·1) of cases of first-episode psychosis could be prevented across the 11 sites, rising to 30·3% (15·2–40·0) in London and 50·3% (27·4–66·0) in Amsterdam. The adjusted incident rates for psychotic disorder were positively correlated with the prevalence in controls across the 11 sites of use of high-potency cannabis (r=0·7; p=0·0286) and daily use (r=0·8; p=0·0109). **Interpretation** Differences in frequency of daily cannabis use and in use of high-potency cannabis contributed to the striking variation in the incidence of psychotic disorder across the 11 studied sites. Given the increasing availability of high-potency cannabis, this has important implications for public health.

2019 Weinberger et al looked at serious psychological distress and daily cannabis use.

ABSTRACT: Daily cannabis use is increasing in the United States (US). Yet, it is not known whether daily cannabis use is disproportionately common, or whether it has increased differentially over time, by mental health status. This study estimated the prevalence of daily cannabis use among adults in the US with and without past-month serious psychological distress (SPD; measured by the Kessler Psychological Distress Scale (K6)) in 2016 and estimated trends in daily cannabis use by past-30-day SPD status from 2008 to 2016. Data were drawn from adults age 18 and older in the 2008-2016 National Survey on Drug Use and Health (combined total analytic sample n = 356,413). Linear time trends of daily cannabis use, stratified by SPD status, were assessed using logistic regression models with continuous year as the predictor.In 2016, past-month daily cannabis use was significantly more common among those with past-month SPD (8.07%), compared to those without past-month SPD (2.66%). Daily cannabis use increased significantly from 2008 to 2016 among those both with and without SPD although use among those with SPD was persistently higher than use among those without SPD over the time period studied. Daily cannabis use is significantly more common among persons with serious psychological distress and is increasing in this group, as well as among those without. Given this increase and the high prevalence of cannabis use among

those with SPD, it may be important to consider potential consequences of this increased use for those with mental health vulnerabilities.

2019 Black et al investigated cannabinoids for the treatment of mental disorders and symptoms of mental disorders – systematic review and meta-analysis. Findings:83 eligible studies (40 randomised controlled trials, n=3067) were included: 42 for depression (23 randomised controlled trials; n=2551), 31 for anxiety (17 randomised controlled trials; n=605), eight for Tourette syndrome (two randomised controlled trials; n=36), three for ADHD (one randomised controlled trial; n=30), 12 for post-traumatic stress disorder (one randomised controlled trial; n=10), and 11 for psychosis (six randomised controlled trials; n=281). Pharmaceutical THC (with or without CBD) improved anxiety symptoms among individuals with other medical conditions (primarily chronic non-cancer pain and multiple sclerosis; SMD −0·25 [95% CI −0·49 to −0·01]; seven studies; n=252), although the evidence GRADE was very low. Pharmaceutical THC (with or without CBD) worsened negative symptoms of psychosis in a single study (SMD 0·36 [95% CI 0·10 to 0·62]; n=24). Pharmaceutical THC (with or without CBD) did not significantly affect any other primary outcomes for the mental disorders examined but did increase the number of people who had adverse events (OR 1·99 [95% CI 1·20 to 3·29]; ten studies; n=1495) and withdrawals due to adverse events (2·78 [1·59 to 4·86]; 11 studies; n=1621) compared with placebo across all mental disorders examined. Few randomised controlled trials examined the role of pharmaceutical CBD or medicinal cannabis. Interpretation There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis. There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed.

2019 Goncalves et al looked at psychotic disorders hospializations associated with cannabis abuse or dependence in a nationwide big data analysis in Portugal. Abstract: We aimed to describe and correlate the hospital panorama of psychotic disorders (PD) with cannabis use (CU) trends in all Portuguese public hospitals. We conducted a retrospective observational study that analysed all hospitalizations that occurred in Portuguese public hospitals from 2000 to 2015. Hospitalizations with a primary diagnosis of PD or schizophrenia were selected based on Clinical Classification Software diagnostic single-level 659. Episodes associated with CU were identified by the International Classification of Diseases Version 9, Clinical Modification code 304.3/305.2 that correspond to cannabis dependence/cannabis abuse.
The number of hospitalizations with a primary diagnosis of PD and schizophrenia associated with CU rose 29.4 times during the study period, from 20 to 588 hospitalizations yearly (2000 and 2015, respectively) with a total of 3,233 hospitalizations and an average episode cost of €3,500. Male patients represented 89.8% of all episodes, and the mean/median age at discharge were 30.66/29.00 years, respectively. From all hospitalizations with a primary diagnosis of PD or schizophrenia, the ones with a secondary diagnosis of CU rose from 0.87% in 2000 to 10.60% in 2015.The increase on secondary diagnosis coding and the change on cannabis patterns of consumption in Portuguese population with an increasing frequency of moderate/high dosage cannabis consumers may explain the rise on PD hospitalizations.

2020 Hengartner et al looked at cannabis use during adolescence and the occurrence of depression, suicidality and anxiety disorder across adulthood. Findings from a longitudinal cohort study over 30 years. Objective To examine the association between cannabis use in adolescence and the occurrence of depression, suicidality and anxiety disorders during adulthood. Methods A stratified population-based cohort of young adults (n = 591) from Zurich, Switzerland, was retrospectively assessed at age 19/20 for cannabis use in adolescence. The occurrence of depression, suicidality and anxiety disorders was repeatedly assessed via semi-structured clinical interviews at the ages of 20/21, 22/23, 27/28, 29/30, 34/35, 40/41, and 49/50. Associations were controlled for various covariates, including socio-economic deprivation in adolescence as well as repeated time-varying measures of substance abuse during adulthood. Results About a quarter (24%) reported cannabis use during adolescence; 11% started at age 15/16 or younger and 13% between the ages of 16/17 and 19/20. In the adjusted multivariable model, cannabis use during adolescence was associated with adult depression (aOR = 1.70, 95%-CI = 1.24–2.32) and suicidality (aOR = 1.65, 95%-CI = 1.11–2.47), but not anxiety disorders (aOR = 1.10, 95%-CI = 0.82–1.48). First use at age 15/16 and younger (as against first use between age 16/17 and 19/20 and no use) and frequent use in adolescence (as against less frequent use and no use) were associated with a higher risk of depression in adult life.Conclusions In this longitudinal cohort study over 30-years, cannabis use during adolescence was associated with depression and suicidality in adult life. Young age at first use and high frequency of use in

adolescence may particularly increase the risk of depression in adulthood. All associations were independent of cannabis abuse and other substance abuse during adulthood.

2020 Smith et al looked at cannabis exposure during critical windows of development: epigenetic and molecular pathways implicated in neuropsychiatric disease. Abstract: Purpose of Review Cannabis exposure during critical windows of development may have intergenerational physiological consequences disrupting epigenetic programming and marks. This review examines the literature relating to pre-gestational and prenatal cannabinoid exposure and its effect on genes and molecular pathways related to the development of psychiatric disease. Recent Findings Developmental cannabis exposure alters epigenetic processes with functional gene consequences. These include potentially heritable alterations in genes and molecular pathways critical for brain development and associated with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), schizophrenia, addiction, and other psychiatric diseases. Summary Cannabis consumption and mental health illness in adolescents and young adults are increasing in the United States (U.S.), and recent studies suggest that cannabis consumption during critical periods of brain development could contribute to mental health illness through epigenetic mechanisms. These findings warrant future studies and consideration by regulators and health communicators.

2020 Kloft et al found that cannabis increases susceptibility to false memory. Absract: With the growing global acceptance of cannabis and its widespread use by eyewitnesses and suspects in legal cases, understanding the popular drug's ramifications for memory is a pressing need. In a double-blind, randomized, placebo-controlled trial, we examined the acute and delayed effects of Δ9-tetrahydrocannabinol (THC) intoxication on susceptibility to false memory in 64 healthy volunteers. Memory was tested immediately (encoding and retrieval under drug influence) and 1 wk later (retrieval sober). We used three different methods (associative word lists and two misinformation tasks using virtual reality). Across all methods, we found evidence for enhanced false-memory effects in intoxicated participants. Specifically, intoxicated participants showed higher false recognition in the associative word-list task both at immediate and delayed test than controls. This yes bias became increasingly strong with decreasing levels of association between studied and test items. In a misinformation task, intoxicated participants were more susceptible to false-memory creation using a virtual-reality eyewitness scenario and virtual-reality perpetrator scenario. False-memory effects were mostly restricted to the acute-intoxication phase. Cannabis seems to increase false-memory proneness, with decreasing strength of association between an event and a test item, as assessed by different false-memory paradigms. Our findings have implications for how and when the police should interview suspects and eyewitnesses.

2020 Hines et al found that users of high potency cannabis were four times more likely to report asssooociated problems. Abstract: **Importance** Cannabis use is consistently linked to poorer mental health outcomes, and there is evidence that use of higher-potency cannabis increases these risks. To date, no studies have described the association between cannabis potency and concurrent mental health in a general population sample or addressed confounding using longitudinal data. **Objective** To explore the association between cannabis potency and substance use and mental health outcomes, accounting for preceding mental health and frequency of cannabis use. **Design, Setting, and Participants** This cohort study used data from the Avon Longitudinal Study of Parents and Children, a UK birth cohort of participants born between April 1, 1991, and December 31, 1992. Present data on outcomes and exposures were collected between June 2015 and October 2017 from 1087 participants at 24 years of age who reported recent cannabis use. **Exposures** Self-reported type of cannabis most commonly used in the past year, coded to a binary exposure of use of high-potency cannabis or lower-potency cannabis. **Main Outcomes and Measures** Outcomes were reported frequency of cannabis use, reported cannabis use problems, recent use of other illicit drugs, tobacco dependence, alcohol use disorder, depression, generalized anxiety disorder, and psychotic-like experiences. The study used secondary data; consequently, the hypotheses were formulated after data collection. **Results** Past-year cannabis use was reported by 1087 participants (580 women; mean [SD] age at onset of cannabis use, 16.7 [3.0] years). Of these, 141 participants (13.0%) reported the use of high-potency cannabis. Use of high-potency cannabis was associated with increased frequency of cannabis use (adjusted odds ratio [AOR], 4.38; 95% CI, 2.89-6.63), cannabis problems (AOR, 4.08; 95% CI, 1.41-11.81), and increased likelihood of anxiety disorder (AOR, 1.92; 95% CI, 1.11-3.32). Adjustment for frequency of cannabis use attenuated the association with psychotic experiences (AOR 1.29; 95% CI, 0.67-2.50), tobacco dependence (AOR, 1.42; 95% CI, 0.89-2.27), and other illicit drug use (AOR, 1.29; 95% CI, 0.77-2.17). There was no evidence of association between the use of high-potency cannabis and alcohol use disorder or depression. **Conclusions and Relevance** To our knowledge, this study provides the first general population evidence suggesting that the use of high-potency cannabis is associated with mental health and addiction. Limiting the availability of high-potency cannabis may be associated with a reduction in the number of individuals who develop cannabis use disorders, the prevention of

cannabis use from escalating to a regular behavior, and a reduction in the risk of mental health disorders.

2020 Weinberger et al investigated cannabis use among US adults with anxiety from 2008 to 2017. Abstract Cannabis use is more common among adults with anxiety. Cannabis legalization is occurring rapidly across the United States (US) and individuals may use cannabis to cope with anxiety. This study investigated whether cannabis use across the US has changed differentially by anxiety status and by state cannabis legalization for medical (MML) and/or recreational use (RML). Methods Public and restricted-use data from the 2004-2017 National Survey on Drug Use and Health, an annual cross-sectional, nationally representative survey of US individuals, were analyzed. The prevalence of past-30-day cannabis use by anxiety status in 2017 was estimated among respondents ages ≥18 (n = 42,554) by sociodemographics and state-level cannabis law. Weighted logistic regressions with continuous year as the predictor for the linear time trend were used to examine the time trends in cannabis use by anxiety and cannabis law status from 2004 to 2017 (total combined analytic sample n = 398,967).Results Cannabis use was consistently two to three times higher among those with high anxiety compared to those with some or no anxiety and was higher in states with RML compared to MML or no MML/RML. Conclusion: Cannabis use has increased over time among those with and without anxiety overall, in MML states, and in states without MML/RML; with a faster increase in cannabis use among those with high anxiety compared to lower anxiety in states with MML. Cannabis use is increasing among American adults overall, yet is disproportionately common among Americans with anxiety especially among those residing in states where cannabis has been legalized.

2020 Miller wrote on the novel insights on cannabis and psychosis. Conclusions Premorbid cannabis use is associated with a dose-dependent increased risk of developing a psychotic disorder. There is evidence in both patients with psychotic disorders and the general population that cannabis use is associated with adverse effects of psychopathology and cognition. Cannabis use and CUDs are highly prevalent throughout the clinical course of illness. Cannabis use is associated with an earlier age of onset of psychosis and more severe impairments in neurocognition. Continued cannabis use after the onset of psychosis is associated with increased risk of illness relapse, longer hospitalizations, and more severe positive psychopathology. There is also evidence for superior efficacy of clozapine for reduction of substance use and negative symptoms in patients with schizophrenia and comorbid cannabis use. Targeted interventions for improved prevention, detection, and treatment are warranted to improve outcomes in this population.

2020 Schrott et al looked a cannabis use inassociation with potential inheritable widespread in autism candidate gene DGAP2 DNA methylation in sperm. Abstract: Parental cannabis use has been associated with adverse neurodevelopmental outcomes in offspring, but how such phenotypes are transmitted is largely unknown. Using reduced representation bisulphite sequencing (RRBS), we recently demonstrated that cannabis use is associated with widespread DNA methylation changes in human and rat sperm. Discs-Large Associated Protein 2 (*DLGAP2)*, involved in synapse organization, neuronal signaling, and strongly implicated in autism, exhibited significant hypomethylation ($p < 0.05$) at 17 CpG sites in human sperm. We successfully validated the differential methylation present in *DLGAP2* for nine CpG sites located in intron seven ($p < 0.05$) using quantitative bisulphite pyrosequencing. Intron 7 DNA methylation and *DLGAP2* expression in human conceptal brain tissue were inversely correlated ($p < 0.01$). Adult male rats exposed to delta-9-tetrahydrocannabinol (THC) showed differential DNA methylation at *Dlgap2* in sperm ($p < 0.03$), as did the nucleus accumbens of rats whose fathers were exposed to THC prior to conception ($p < 0.05$). Altogether, these results warrant further investigation into the effects of preconception cannabis use in males and the potential effects on subsequent generations.

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One cannot vote for a medicine

Scientific approval basis is essential

(Distributed to all UK MPs Feb. 2000.)

E.U. Rules[1] set out various criteria for the acceptance of a drug for medical use, these include:

1. All active ingredients have to be identified and their chemistry determined. They have to be tested for purity with limits set for all impurities including pesticides, microbes & fungi and their products. These tests have to be validated and reproduced if necessary in an official laboratory.

The cannabis plant contains some 400 chemicals, a multiplicity of ingredients that vary with habitat – impossible to standardise and often contaminated with microbes, fungi or pesticides.[2]

2. Animal testing will include information on fertility, embryo toxicity, immuno-toxicity, mutagenic and carcinogenic potential. Risks to humans, especially pregnant women and lactating mothers, will be evaluated.

Cannabis has been shown to reduce sperm production.[3] Babies born to cannabis-using mothers are smaller, have learning and behavioural problems and are 10 times more likely to develop one form of leukaemia.[4] The immune system is impaired.[5] Smoking herbal cannabis results in the inhalation of three times as much tar as from a tobacco cigarette.[6]

3. Adequate safety and efficacy trials must be carried out. They must state the method of administration and report on the results from different groups, i.e. healthy volunteers, patients, special groups of the elderly, people with liver and kidney problems and pregnant women. Adverse drug reactions (ADR) have to be stated and include any effects on driving or operating machinery.

Presumably it is envisaged that cannabis would be smoked. No medicine prescribed today is smoked. Concentration, motor-co-ordination and memory are all badly affected.[7] Changes in the brain have been observed[8] and U.S.A. clinics are now coping with more cases of psychosis caused by cannabis than by any other drug. It is essential to note that the content of THC (Tetrahydrocannabinol – the psychoactive ingredient in cannabis) is on average ten times higher than it was in the 1960s.[9] The fat-soluble THC lingers in the body for weeks[10] and the ability to drive safely is impaired for at least 24 hours after smoking cannabis.[11] Although ten times as many people use alcohol, cannabis is implicated in a similar number of road accidents.[12]

4. The drug must be accepted by qualified experts. Their detailed reports need to take account of all the relevant scientific literature and the potential of the drug to cause dependence.

There are numerous accounts of both psychological and physical dependencies in cannabis use.[13] Some 77,000 people are admitted annually to hospitals in U.S.A for cannabis dependence, 8,000 of them as emergencies.[14] To date there are over 12,000 scientific publications relating to cannabis.[15]

THC has already undergone all the medical tests. It is available on prescription in tablet form for the relief of nausea from chemotherapy and appetite stimulation in AIDS patients. However marinol (USA) and nabilone (UK), synthetic forms of THC and identical in action to it, are not the first drugs of choice among oncologists in Washington D.C. ranking only 9th in the treatment of mild nausea and 6th for more severe nausea.[16] The warning on nabilone reads,

'THC encourages both physical and psychological dependence and is highly abusable. It causes mood changes, loss of memory, psychoses, impairment of co-ordination and perception, and complicates pregnancy".

Other Cannabinoids: Cannabis contains around 60 cannabinoids that are unique to the plant. Some of these could be similarly extracted, purified and tested for safety and efficacy. In the report "Therapeutic Uses Of Cannabis" (BMA, 1997) the British Medical Association said,

"It is considered here that cannabis is unsuitable for medical use. Such use should be confined to known dosages of pure or synthetic cannabinoids given singly or sometimes in combination".

WHAT THE EXPERTS HAVE SAID

Dr Eric Voth MD, FACP (Chairman of the International Drug Strategy Institute) said in a letter to the editor of the New England Journal of Medicine (Jan 1997), **"Long term effects aside, contaminants, purity, standardisation of dose etc are all reasons to not use an impure herb as a medicine. Whether terminal or not, should we support smoking Foxglove plant to obtain Digoxin for heart failure, or Yew tree bark to obtain Taxol for breast cancer? If so, then supporters of smoked marijuana better**

be ready to support smoking tobacco for weight control and anxiety. We must have compassion for the sick and suffering and we must offer them reliable and quality medicine, not crude substances that threaten their well being".

Glaucoma: The pressure in the eye caused by this condition can be reduced by smoking cannabis but Professor Keith Green, Director of Ophthalmic Research at the Medical College of Georgia said some 6 'joints' a day would be required, rendering the patient effectively 'stoned' and incapable of useful activities.

Multiple Sclerosis: Dr Donald Silberg, Chief of Neurology, Pennsylvania school of Medicine said, "I have not found any legitimate or scientific works which show that marijuana is medically effective in treating Multiple Sclerosis or spasticity. The use of marijuana especially for long-term treatment would be worse than the illness itself".

DOES THE PUBLIC REALLY WANT THIS?

Nov 1996: Proposition 200 permitted physicians in Arizona to prescribe pure marijuana with no limitation on the age of the patient or disorder involved.

Jan 1997: A public opinion poll revealed that 85% of registered voters believed that proposition 200 should be changed and 60% wanted it repealed, 70% said it gave children the impression that drugs are OK for recreational use.[17]

HOW DID THE CAMPAIGN GET STARTED?

In 1979: Keith Stroup, an American pot-using lawyer, and the then head of NORML (National Organisation for Reform of Marijuana Laws) said, "We will use the medical marijuana argument as a red herring to give pot a good name."[18]

Early 1990s Richie Cowan, Stroup's successor at NORML, echoed him when he said, "Medical marijuana is our strongest suit. It is our point of leverage which will move us toward the legalisation of marijuana for personal use."[19]

A Last Word From Dr Eric Voth

"We cannot by-pass the usual safety and efficacy process of the FDA (Food and Drugs Administration) because of the hue and cry of a self-preserving drug culture which seeks to add medicinal applications of marijuana, mixed messages of legalisation of illegal drugs, harm reduction and tolerance of drug use."[20]

Update April 2008. A paper by H Kalant was entitled "Smoked Marijuana as Medicine: Not Much Future". It concluded, 'The lack of convincing evidence thus far makes it unlikely that future studies will demonstrate any significant advantage of smoked marijuana over oral or parenteral use of pure cannabinoids. Therefore, no persuasive reason is evident for running the added risks associated with smoking. (21)

2013 Dr Gregory Pike Director Adelaide Centre for Bioethics and Culture May 2013 'Medical Marijuna – a Dopey Idea?

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Drug Education in UK Schools (2006)

Common sense surely dictates that drug education in schools should be based on prevention, that teachers will be doing everything they can to try to stop children from ever starting to use drugs. And in the government documents, Tackling Drugs Together and its various updates, prevention is indeed the stated aim. Sadly there is a great lack of common sense today.

For the past 15 years or so, the philosophy behind drug education has been one of harm reduction: - "Children will use drugs anyway, we must tell them how to do it safely and give them *informed choices".* Harm reduction has its legitimate place when dealing with a drug user on a one to one basis to lessen the risks, e.g. inhaling the fumes from heated heroin instead of injecting, with a view to getting him or her to stop. It has *no* place in the classroom.

If we analyse the statement we can begin to understand why drug use has risen and is still rising. "Children will use drugs anyway" is simply not true. Drug use is *not* the norm. 30 or 40% may *try* them, but how many try cigarettes, 95%? Regular drug taking in Britain today is around 10%. "We must tell them how to do it safely". There is no guaranteed safe way to take any drug, legal or illegal, and the phrase "informed choices" is indefensible. Currently they are not being properly informed, harm reduction literature *always* plays down the risks of cannabis. Nor should there be a choice, drug taking is illegal. Do we let them choose to spray graffiti or pilfer from shops, other illegal activities? Children are not miniature adults. Their brains will not be fully developed till they are in their twenties. They are incapable of making critical life decisions. QCA and DfES guidelines on drug education both advocate choice at key stage 2, 7 to 11 year olds! In the entire QCA document I failed to find the word prevention. The harm reduction approach does not *tackle* drugs it *accommodates* or even *condones* them.

On the government's drug information website FRANK the warnings of the dangers of drugs especially cannabis are woefully inadequate and sometimes inaccurate. "There is minimal risk of physical dependence, and there should be no problem stopping (unless you get addicted to the tobacco)". Some users have written of the almost impossible task of stopping and the dreadful withdrawal symptoms they have experienced. Lots of very dubious risk reduction tips are given, "Give one drug plenty of time to kick in or wear off before taking another" is just one of their "gems" of advice. One of my sixth formers who phoned FRANK pretending to be a pot user, was told that mixing alcohol and cannabis would simply exaggerate the effects, in fact it could be fatal, they are both depressants. Stronger varieties, he was told, would make everything crisper and brighter and he would feel more relaxed. In reality he could suffer an acute psychotic episode. Drugscope, the charity advising the government, does not want people with small amounts of any drugs in their possession to be arrested. The organisation "Connexions" sent out a leaflet on cannabis to schools. It mimicked a "Rizla" packet, said virtually nothing about the dangers but had masses of advice on risk reduction. My sixth form thought it positively encouraged drug use. I succeeded in getting it banned.

Talking to a roomful of parents whose children were all psychotic or schizophrenic because of cannabis was one of the most harrowing evenings I have spent. Shattered families, wasted talent.

Our children are being betrayed. As adults we have a duty to protect our vulnerable offspring. We don't let them eat poisonous berries, or cross main roads till they are old enough, why do we abandon them to drugs?

Clearly something has to be done.

The whole thrust of drug education must move from harm reduction to prevention. Prevention has always been better than cure and always will be. To quote from Dr Patrick Dixon's book, "The Truth about Drugs" 1998, "The majority of teenagers do not use any illegal drugs and never have – the biggest weapon we have in prevention is normalisation, helping those under pressure to see the truth, which is that abstention from illegal drugs and tobacco is the norm at any age of childhood, adolescence or adulthood".

Prevention worked in the USA. The idea that drug taking was not the norm was hammered home. This was the much ridiculed "Just say no" campaign. Between 1979 and 1991, the number of drug users fell from 23 to 14 million. Cannabis and cocaine use halved. It's working now. Under the new drug tsar, John Walters, they have seen an 11% decline in drug use over 2 years, the target was 10%. Surveys show that about 70%

of youngsters are deterred by concern over physical and psychological damage, 60% by parental disapproval, around half are afraid of becoming addicted or losing self control, and 40% by the law.

Prevention is not only "Just say no" and never has been. Everyone in America co-operated, teachers, police, parents, social and youth workers, customs officers, the children themselves. The message went out loud and clear that drug taking was not normal, not acceptable and most definitely harmful.

I have found that, if I explain to pupils, simply and scientifically, using diagrams of cells, how mind-altering drugs affect the brain and body, relate these to the adverse health, psychological and social consequences, lost educational opportunities and employment prospects, they begin to realise just how futile that lifestyle would be. I know, they tell me. The controversies around drugs are also aired, the medical arguments and "gateway" theory in the case of cannabis, the views of libertarians and legalisers, effects on family and friends, why the law is in place and the effects of its relaxation. A surprising number of children wanted "shock horror stories" when asked what would put them off drugs but by far the largest request was for facts about their health, put over in a non-patronising way. A multi-faceted approach will hopefully deter most children. I am not a fan of drug education games. "Pretend you're a drug dealer" to my mind sends a very questionable message, and playing around with syringes, foil, matches, cigarette papers and drink bottles as suggested in QCA guidelines fills me with horror.

More difficult to change is the culture of acceptance of drugs now widespread in our society. Years of campaigning against tobacco has eventually seen smoking as a minority and largely socially unacceptable habit. But everyone must pull together. Attitudes to drugs vary widely, there is a lot of hypocrisy and double-standards. Kate Moss at first was condemned for her cocaine use then suddenly most of her lucrative contracts were restored. T-shirts, bags and jackets promote cannabis. Pop songs glamorise drugs and charities like Release and Transform actively lobby for legalisation.

The Swedes have the right idea. *All* drugs are treated alike. There are no Classes, drug use is very low. The question of re-classifying cannabis would never have arisen. Admissions of cannabis users to hospitals in the UK for mental illnesses have risen by 40% since it was suggested.

Children *need* and *want* rules and regulations. The only way they feel safe and secure is when they have boundaries to kick against. Teachers who fail to control classes gain no respect. I often hear children use their parents as an excuse when they don't want to do something. A few years ago I listened to a young girl in The House of Lords where I was taking part in a conference on cannabis, she said, " …you adults have to say that you care, that you feel strongly about what we do – don't leave it as a choice. If you don't want us to do drugs then say so – and why. You don't ask us to choose whether to steal, or attack people, so why leave us to choose about drugs?"

It was like a breath of fresh air.