External Contributions to the St. Kitts and Nevis National Cannabis Commission

Cannabis - Dr. Lisa Skerritt

“Prohibition turned law-abiding citizens into criminals, made a mockery of the justice system, caused illicit drinking [drug use] to seem glamorous and fun, encouraged neighborhood gangs to become national crime syndicates, permitted government officials to bend and sometimes even break the law, and fostered cynicism and hypocrisy that corroded the social contract all across the country.”

“The key problem with Prohibition and the War On Drugs is that, although they do little to change the behavior of substance abusers, they create a gigantic black market that in turn causes crime, corruption and disease on a massive scale.” - Ken Burns’ three-part PBS series Prohibition

“The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. You understand what I’m saying? We knew we couldn’t make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.” - John Ehrlichman, former Nixon domestic affairs adviser

“Penalties against possession of a drug should not be more damaging to an individual than the use of the drug itself; and where they are, they should be changed. Nowhere is this more clear than in the laws against possession of marijuana in private for personal use... Therefore, I support legislation amending Federal law to eliminate all Federal criminal penalties for the possession of up to one ounce [28g] of marijuana.” — Jimmy Carter

For 9000 years, hemp was earth’s most important commodity, and in the last 60 years, it has been earth's most persecuted commodity. The global tide is turning concerning marijuana legalization. Countries like Israel and Portugal, and states like Colorado, Oregon and Washington have proven that allowing responsible adults to legally purchase marijuana, gives money to classrooms, not cartels; creates jobs, not addicts; and boosts the economy, not the prison population. There is a global revolution happening, fueled by knowledge gained from the internet – the genie cannot be put back into the bottle.

Legislative Changes

- Cannabis prohibition began with no scientific, medical or social justification, and was initiated by the United States of America to harass and punish racial minorities.
- Cannabis prohibition causes social and economic harms, and criminalises thousands of citizens of the Federation for no benefit.
- Cannabis prohibition finances organised crime.
- Cannabis can provide food, medicine, fibre, fuel and building materials.
- Cannabis is a proven safe medicine that can effectively treat a wide variety of ailments.

We call upon the Government to:

- Repeal the prohibition on the possession and personal cultivation of cannabis;
- Remove cannabis from the Drug Abuse (Prevention and Control) Act;
- Allow farmers to harvest and sell cannabis and cannabis-based products;
- Facilitate the development of a legal cannabis market for local consumption and export;
- For those convicted for a cannabis offence under the Drug Abuse (Prevention and Control) Act, on a case by case basis: Grant full pardon and amnesty for past offences, expunge criminal records and release all prisoners currently serving time.

Crime Against Humanity

Cannabis prohibition is one of the most heinous acts against humanity in history, and it has been perpetrated mostly against people of colour. This is one of the biggest issues of our generation and is connected to the corporate greed that is destroying the planet, poisoning our food, and killing us with drugs. Tens of millions of lives have been destroyed, and families torn apart in the prohibition and criminalizing of this healing plant. The US government is perpetrating one of the greatest crimes against humanity in history, and our governments have been helping them to enslave people of colour and poor people for their own financial gain, and because of their willful ignorance.

The US government has known since 1947 that cannabis successfully treats childhood epilepsy in at least 50% of cases. Thousands of children have died extremely agonizing deaths. Having up to 400 grand mal seizures per day until they die from brain damage. They let these children suffer and die because of their greed.

http://antiquecannabisbook.com/chap03/Epilepsy/Epilepsy-P1.htm

1. Cannabis prohibition arose from:
    a. Corporate Greed & Special Interests
    b. Endemic Corruption
    c. Systemic Racism
2. Cannabis prohibition is related to major global issues:
    a. Black Market Crime
    b. Climate Change
    c. Environmental Pollution
    d. Deforestation
    e. Big Pharma
    f. Agricultural Industry, Oil Industry
    g. Privatized Prisons
3. Prohibition has enormous social costs - from wasted resources to ruined lives
4. The War On Drugs has been a colossal failure – regulating drugs, and harm reduction models more effective
5. Prohibition is ineffective and counterproductive - The benefits of criminalization are minuscule to nonexistent
6. Crime reduction - Prohibition linked to crime – 78% increase of crime during alcohol prohibition
7. Prohibition is racist - enforcement is inherently biased
8. Cannabis has legitimate medical effects - Hundreds of medicinal uses
9. Legalization does not lead to increased use
10. Cannabis is less harmful than alcohol or tobacco

11. Legalizing and regulating makes it less accessible to youth
12. Cannabis prohibition and its enforcement - one of the greatest crimes against humanity in history
13. Cannabis has been a cornerstone of human civilization for 9,000 years

Over 27,000 people die every day from alcohol and tobacco.

Alcohol stats

Alcohol is responsible for 3.3 million deaths per year. One in 10 deaths among working-age adults aged 20–64 years are due to excessive alcohol use. Of the top 19 global health concerns, alcohol is ranked #3, and is greater than unsafe water, high blood pressure, tobacco, obesity and illicit drugs (ranked #18).

Excessive alcohol use is a leading cause of preventable death. These deaths were due to health effects from drinking too much over time, such as breast cancer, liver disease, and heart disease, and health effects from consuming a large amount of alcohol in a short period of time, such as violence, alcohol poisoning, and motor vehicle crashes. Excessive alcohol use shortened the lives of those who died by about 30 years. The impact of these deaths affects the nation's economy and the sustainability of families. Excessive drinking cost the United States about $224 billion, or $1.90 per drink, in 2006

Tobacco stats

One in 10 deaths around the world is caused by smoking, according to a major new study that shows the tobacco epidemic is far from over and that the threat to lives is spreading across the globe. There were nearly one billion smokers in 2015, in spite of tobacco control policies having been adopted by many countries. That number is expected to rise as the world's population expands. One in every four men is a smoker and one in 20 women. Their lives are likely to be cut short – smoking is the second biggest risk factor for early death and disability after high blood pressure. The researchers found there were 6.4m deaths attributed to smoking in 2015, of which half were in just four populous countries – China, India, USA, and Russia.

Opioids Someone dies in the US every 10 minutes from an unintentional pharmaceutical overdose. Over four million Americans misuse opioids each month, at a societal cost of $80 billion annually. 300 million prescriptions were written in 2015 in the U.S., which has a population of 323 million. This is reflected in the fact that 80 percent of the world's opioids are consumed in the U.S., which has 5 percent of the world's population.

Drug overdose is the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015. Opioid addiction is driving this epidemic, with 20,101 overdose deaths related to prescription pain relievers, and 12,990 overdose deaths related to heroin in 2015.

Myths about cannabis

Gateway drug – has actually been shown to help opium addicts recover from opiates. Addictive – less than most...alcohol, cigarettes, sugar, gambling, worrying Causes mental problems/psychosis in youth – not proven Causes brain damage/kills brain cells – heals the brain and regenerates neurons Causes lung damage – only extremely heavy smoking Causes overdose – does not affect respiratory system Harmful to health – 116 times less toxic than alcohol Legalizing would increase teen use – teen use in Colorado dropped Cannabis use leads to crime – false. Prohibition leads to crime, black markets and corruption

Primary issues:

1. Medicinal Cannabis – Hundreds of peer reviewed studies showing its efficacy at treating numerous untreatable and terminal diseases, including 18 types of cancer to date. Until it was made illegal, cannabis was one of the most used medicines, and the #1 medicine for treating pain. 50% of medicine sold in the US in the 19th century contained cannabis.
2. Industrialized Hemp – makes 50,000+ products currently being made with petrochemicals and trees… https://ministryofhemp.com/blog/hemp-products-list/
3. Criminalizing innocent civilians - War on Drugs & Industrial Prison Complex – (mostly of colour) and destroying their lives. Loss of job/career if incarcerated. People with minor marijuana charges taking up space in prison alongside serious criminals - teaching them to be hardened criminals; costs money; makes prisons overcrowded.
4. Economic Benefits – fastest growing industry in the US, poised to be one of the biggest in the world– job creation, tax revenue, exportation; career opportunities for youth
5. Crime reduction – eliminates black market, creates career opportunities for youth
6. Environmental Impact - Hemp needs no pesticides or fertilizers, and actually puts nutrients back into the soil. Its prohibition is one of the reasons for our current this ecological crisis. Hemp can make anything petrochemicals and trees can make, and better. Over 50,000 products and counting, including biodegradable plastic. Some of the impacts of prohibition are increased Co2 into the atmosphere, polluted oceans, lakes and rivers, and destruction of most of the forests in the contiguous USA. Corporate greed and its connection to environmental damage and mortality rates.
7. Civil Rights Issue – criminalizing one of the most beneficial herbs; the War On Drugs was created to persecute blacks and hippies in the 70's and 80's – as per former Richard Nixon aide John Ehrlichman "The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. You understand what I'm saying?" Ehrlichman told Baum. "We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did.", which developed into the Prison Industrial Complex in the US – modern day slavery – privatized prisons that are work farms
8. Pharmaceutical Crisis – Rx deaths leading cause of accidental death in the US – every 19 mins; iatrogenic one of the leading causes of death, possibly the leading cause. Unintentional Rx overdoses – leading cause of accidental death in the US. The CDC is calling it an "Epidemic". Opiate crisis costing the US $78 billion per year. More people are now addicted to opiates than to heroin, cocaine & crystal meth combined. More fatalities are due to opiates than to heroin, cocaine & crystal meth combined. States where cannabis is legal – 25% drop in accidental Rx deaths. US spends $600 billion annually on pain management (Cancer = $200 billion) 30% GP visits.
9. Hypocrisy – Cigarettes kill 5 mil people/year; Alcohol kills 2 mil people/yr; Half the food in the supermarket - processed foods, sugar – heart disease leading cause of death, cancer 2nd leading cause of death
10. Social Benefits – reduction in teen use, car fatalities, pharmaceutical overdoses, spousal abuse
11. Relations with Law Enforcement – the internet allows everyone to have access to the truth. The police will become less and less respected for enforcing these ridiculously unfair and hypocritical laws, while being complicit in one of the greatest crimes against humanity - More people have been harmed and killed for this plant than suffered and died from the Atlantic slave trade, where my ancestors were also victimised and persecuted for greed and bigotry. Add to that the tens of millions of people have suffered and died from cancer and other terminal illnesses because it has been illegal for 80 years. And the

children with epilepsy who have suffered while the FDA has known since 1943 that it cures Dravet's (grand mal seizures).

12. Historical Importance – one of the oldest cultivated crops ~ 9,000 years - Oldest known records of hemp farming go back 5000 years in China, although hemp industrialization probably goes back to ancient Egypt. 8,000+ BCE Use of hemp cord in pottery identified at ancient village site dating back over 10,000 years, located in the area of modern day Taiwan. Finding hemp use and cultivation in this date range puts it as one of the first and oldest known human agriculture crops. This point was also touched on by Carl Sagan in 1977 when he proposed the possibility that marijuana may have actually been world's first agricultural crop, leading to the development of civilization itself. 6,000 BCE Cannabis seeds and oil used for food in China. 4,000 BCE Textiles made of hemp are used in China and Turkestan. 2,737 BCE First recorded use of cannabis as medicine by Emperor Shen Neng of China. For thousands of years, 90% of all ships' sails and rope were made from hemp. The word 'canvas' comes from the Middle English word "canevas" which comes from the Latin word cannabis. 80% of all textiles, fabrics, clothes, linen, drapes, bed sheets, etc., were made from hemp until the 1820s, with the introduction of the cotton gin. The first Bibles, maps, charts, Betsy Ross's flag, the first drafts of the Declaration of Independence and the Constitution were made from hemp. Rembrandt's, Van Gogh's, Gainsborough's, as well as most early canvas paintings, were principally painted on hemp linen. Henry Ford's first Model-T was built to run on hemp gasoline and the car itself was constructed from hemp! On his large estate, Ford was photographed among his hemp fields. The car, 'grown from the soil,' had hemp plastic panels whose impact strength was 10 times stronger than steel. Modern cars and planes are being made and powered from hemp.
13. Religious Importance - The first mention of kaneh-bosm in the Old Testament appears with the prophetshaman Moses. The sacred character of hemp in biblical times is evident from Exodus 30:22-33, where Moses was instructed by God to anoint the meeting tent and all its furnishings with specially prepared oil, containing hemp.

The War On Drugs

The reality of the war on drugs is that it is not based on scientific evidence. Instead, it is based on a dark history of oppression, racism, and political corruption.

In spite of some form of cannabis being legal in some fashion in 29 states and Washington D.C., the government still violently and with extreme prejudice continues to seek out those who dare possess it.

If the CDC calculated the number of deaths inflicted by police while enforcing marijuana laws, that number would certainly be shocking and could even be deemed a risk to public health. Marijuana is, indeed, dangerous, but only because of what can happen to you if the police catch you with it.

Nothing highlights the hypocrisy, immorality, and sheer idiocy of the drug war quite like marijuana prohibition. Here we have a medicine that kills cancer cells, saves the lives of countless epileptic children, heals broken bones, relieves pain, treats PTSD, is not dangerous, and exhibits a variety of other incredible benefits – yet the state will kill you over it.

Drug War Statistics

- Amount spent annually in the U.S. on the war on drugs: More than $51,000,000,000
- Number of arrests in 2015 in the U.S. for drug law violations: 1,488,707
- Number of these arrests that were for possession only: 1,249,025 (84 percent)
- Number of people arrested for a marijuana law violation in 2015: 643,121
- Number of those charged with marijuana law violations who were arrested for possession only: 574,641

(89 percent)

- Number of Americans incarcerated in 2014 in federal, state and local prisons and jails: 2,224,400 or 1 in every 111 adults, the highest incarceration rate in the world
- Proportion of people incarcerated for a drug offense in state prison who are black or Latino, although these groups use and sell drugs at similar rates as whites: 57 percent
- Number of states that allow the medical use of marijuana: 28 + District of Columbia
- Number of states that have approved legally taxing and regulating marijuana: 8 (Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon and Washington)
- Number of people killed in Mexico's drug war since 2006: 100,000+
- Number of students who have lost federal financial aid eligibility because of a drug conviction: 200,000+
- Number of people in the U.S. who died from a drug overdose in 2015: 52,404
- Tax revenue that drug legalization would yield annually, if currently-illegal drugs were taxed at rates comparable to those on alcohol and tobacco: $46.7 billion

Harry J. Anslinger started the anti-marijuana movement on nothing but racism

Harry J. Anslinger quotes: ...the primary reason to outlaw marijuana is its effect on the degenerate races.

Marihuana leads to pacifism and communist brainwashing.

Most marijuana smokers are Negroes, Hispanics, jazz musicians, and entertainers. Their satanic music is driven by marijuana, and marijuana smoking by white women makes them want to seek sexual relations with Negroes, entertainers, and others. It is a drug that causes insanity, criminality, and death -- the most violence-causing drug in the history of mankind.

Reefer makes darkies think they're as good as white men.

You smoke a joint and you're likely to kill your brother.

Endocannabinoid System

1. The endocannabinoid system was discovered in the late 1980s when researchers were studying how THC interacted with the body. The ECS would soon be considered more significant than all other neuroscience discoveries combined.
2. In the early 1990s another amazing discovery was made when researchers found two endogenous compounds that bind just like THC with the ECS. These THC-like cannabinoids, produced by our own bodies, are respectively called anandamide and AG-2.
3. It eventually became clear that the receptors which comprised the ECS were the most prevalent neurotransmitters throughout the brain and also found in the organs, bones, and skin.
4. Scientists have learned that the ECS plays a direct role in homeostasis, which means that it regulates every metabolic process in the body to keep things running as they should. As Dr. Sunil Aggarwal pointed out during the Cannabis Health Summit, the ECS plays a role in processes such as:

- Mood regulation
- Appetite
- Memory
- Inflammation
- Pain perception
- Muscle tone and movement
- Extinction of traumatic memory
- Protection of nerves and brain tissue
- Bone growth
- Tumor regulation
- Baby breast-feeding reward
- Stress management

- Eye pressure
- Gastrointestinal motility
- Seizure activity
- And many others

5. When we don't have enough endocannabinoids in our body, we call this clinical endocannabinoid deficiency – which medical researchers are connecting to a number of ailments including previously untreatable illnesses like irritable bowel syndrome or fibromyalgia or migraines. When the ECS isn't healthy, any number of things can go wrong. The cannabinoids in cannabis can helps us bolster the ECS, which is why the herb is so effective for so many different ailments.
6. In addition to endogenous and plant-based cannabinoids, attempts have been made to stimulate the ECS with synthetic cannabinoids such as Marinol, which is the synthetic version of THC. While some patients continue to benefit from this FDA-approved drug, the side effects can be very unpleasant for others.
7. Despite knowledge of the ECS and its relationship with cannabis, governments have maintained severe restrictions on the study and legal access of this plant. In 2014 alone the U.S. government locked up 700,000 people for cannabis all the while knowing the importance of this plant acting on the ECS.
8. Pharmaceutical companies meanwhile are permitted to attempt cracking the ECS in other ways, creating chemical concoctions with often times ineffective, harsh or even fatal results. For example, between 1999 and 2014 the number of opioid prescriptions quadrupled. The number of opioid-related deaths also quadrupled during that time span according to the CDC.
9. People have been using cannabis for over 10,000 years (without a single fatal overdose ever being recorded), and some estimates have the ECS first developing at about 500 million years ago!
10. Many medicals school continue to overlook the ECS, however this is starting to change now that we have the first science-based medical cannabis textbook.
11. Almost every animal, with the exception of insects, has an endocannabinoid system.

The endocannabinoid system plays a hand in many of the body's normal functions. The body contains two major endocannabinoids, arachidonylethanolamine (AEA), nicknamed anandamide from the Sanskrit word for "bliss," and 2-arachidonylglycerol (2-AG). CB1 is the receptor in the brain where endocannabinoids influence short-term memory, pain, emotion, hunger and other basic human feelings. When these endocannabinoids are at proper levels, the body is able to function well. When they are out of balance, however, they can affect numerous systems within the body. It is thought that an endocannabinoid deficiency is responsible for many of the hard-to-treat illnesses alleviated by medical marijuana, that are currently increasing in today's world, and show improvement with the treatment of cannabinoids found in cannabis.

Clinical endocannabinoid deficiency (CECD)

The endocannabinoid system is largest neurotransmitter system in the body. In fact, it is larger than all the others put together. The endocannabinoid system is divided into neurotransmitters and receptors. Neurotransmitters carry messages between the body and brain. In order to convey these messages, the neurotransmitter needs to attach to a transmitter that then takes it to where it needs to go. For example, when your stomach is empty, neurotransmitters located in the digestive system lock onto a receptor and travel to the brain. When that specific chemical reaches the brain, the brain releases hunger signals that tell you it is time to eat. This message system is involved in nearly every type metabolic function. An endocannabinoid deficiency can result in one of two ways. First, the body may not produce enough, or it may produce too much, of the endocannabinoid itself. A second way that things can go wrong is that the receptors fail to bond with the

message chemicals and therefore the message does not reach the brain. In either case, the messages become jumbled and the body responds incorrectly. This can result in conditions such as chronic migraines, fibromyalgia, irritable bowel syndrome (IBS) and other chronic conditions that appear to have no easily recognizable cause.

The miscommunication of the endocannabinoids often results in:

- Extreme pain
- Digestive disorders
- Chronic fatigue
- Mood disorders

Each of these disorders is often co-morbid (or occurring together) and the cause is thought to be an irregularity in the endocannabinoid system.

Medicinal

- 700 MEDICINAL USES OF CANNABIS SORTED BY DISEASE
  - http://www.encod.org/info/700-MEDICINAL-USES-OF-CANNABIS.html
- Over 100 Scientific Studies Agree: Cannabis Annihilates Cancer
  - http://expand-your-consciousness.com/100-scientific-studies-agree-cannabis-annihilates-cancer/?t=THS
- 60 Peer-Reviewed Studies on Medical Marijuana
  - http://medicalmarijuana.procon.org/view.resource.php?resourceID=000884

- Multiple Sclerosis
- Tourette Syndrome
- Pain
- Obsessive Compulsive Disorder
- Brachial Plexus Neuropathies
- Insomnia
- Multiple Splasticity
- Memory Disorders
- Social Anxiety Disorders
- Amyotrophic Lateral Sclerosis
- Inflammatory Bowel Disease
- Cancer
- Opiate Addiction
- Anorexia
- Bladder Dysfunction
- Bronchial Asthma
- Chemotherapy-induced Harm
- Constipation
- Crack Addiction
- Dementia
- Fibromyalgia
- Glaucoma
- Heroin Addiction
- Lymphoma
- Nausea
- Neuropathy
- Obesity
- Phantom Limb
- Spinal Cord Injuries
- Endotoxemia
- Myocardia Infarction (Heart Attack)
- Oxidative Stress
- Diabetes: Cataract
- Tremor
- Cardiac Arrhythmias
- Fatigue
- Fulminant Liver Failure
- Low Immune Function
- Aging
- Alcohol Toxicity
- Allodynia
- Arthritis: Rheumatoid
- Ascites
- Atherosclerosis
- Diabetes Type 1
- High Cholesterol
- Liver Damage
- Menopausal Syndrome

- Morphine Dependence
- Appetite Disorders
- Auditory Disease
- Dystonia
- Epstein-Barr infections
- Gynecomasia
- Hepatitis
- Intestinal permeability
- Leukemia
- Liver Fibrosis
- Migraine Disorders
- Oncoviruses
- Psoriasis
- Thymoma

Nausea and Vomiting Treatment of side effects associated with antineoplastic therapy is the indication for cannabinoids which has been most documented, with about 40 studies (THC, nabilone, other THC analogues, cannabis). Most trials were conducted in the 1980s. THC has to be dosed relatively highly, so that resultant side effects may occur comparatively frequently. THC was inferior to high-dose metoclopramide in one study. There are no comparisons of THC to the modern serotonin antagonists. Some recent investigations have shown that THC in low doses improves the efficacy of other antiemetic drugs if given together. In folk medicine cannabinoids are popular and are often used in other causes of nausea including AIDS and hepatitis.

Anorexia and Cachexia An appetite enhancing effect of THC is observed with daily divided doses totalling 5 mg. When required, the daily dose may be increased to 20 mg. In a long-term study of 94 AIDS patients, the appetite-stimulating effect of THC continued for months, confirming the appetite enhancement noted in a shorter 6-week study. THC doubled appetite on a visual analogue scale in comparison to placebo. Patients tended to retain a stable body weight over the course of seven months. A positive influence on body weight was also reported in 15 patients with Alzheimer's disease who were previously refusing food.

Spasticity In many clinical trials of THC, nabilone and cannabis, a beneficial effect on spasticity caused by multiple sclerosis or spinal cord injury has been observed. Among other positively influenced symptoms were pain, paraesthesia, tremor and ataxia. In some studies, improved bladder control was observed. There is also some anecdotal evidence of a benefit of cannabis in spasticity due to lesions of the brain.

Movement Disorders There are some positive anecdotal reports of therapeutic response to cannabis in Tourette's syndrome, dystonia and tardive dyskinesia. The use in Tourette's syndrome is currently being investigated in clinical studies. Many patients achieve a modest improvement; however, some show a considerable response or even complete symptom control. In some MS patients, benefits on ataxia and reduction of tremor have been observed following the administration of THC. Despite occasional positive reports, no objective success has been found in parkinsonism or Huntington disease. However, cannabis products may prove useful in levodopa-induced dyskinesia in Parkinson disease without worsening the primary symptoms.

Pain Large clinical studies have proven analgesic properties of cannabis products. Among possible indications are neuropathic pain due to multiple sclerosis, damage of the brachial plexus and HIV infection, pain in rheumatoid arthritis, cancer pain, headache, menstrual pain, chronic bowel inflammation and neuralgias. Combination with opioids is possible.

Glaucoma In 1971, during a systematic investigation of its effects in healthy cannabis users, it was observed that cannabis reduces intraocular pressure. In the following 12 years, a number of studies in healthy individuals and glaucoma patients with cannabis and several natural and synthetic cannabinoids were conducted. cannabis decreases intraocular pressure by an average 25-30%, occasionally up to 50%. Some non-psychotropic

cannabinoids, and to a lesser extent, some non-cannabinoid constituents of the hemp plant also decrease intraocular pressure.

Epilepsy The use in epilepsy is among its historically oldest indications of cannabis. Animal experiments provide evidence of the antiepileptic effects of some cannabinoids. The anticonvulsant activity of phenytoin and diazepam have been potentiated by THC. According to a few case reports from the 20th century, some epileptic patients continue to utililize cannabis to control an otherwise unmanageable seizure disorder.

Asthma Experiments examining the anti-asthmatic effect of THC or cannabis date mainly from the 1970s, and are all acute studies. The effects of a cannabis cigarette (2% THC) or oral THC (15 mg), respectively, approximately correspond to those obtained with therapeutic doses of common bronchodilator drugs (salbutamol, isoprenaline). Very few patients developed bronchoconstriction after inhalation of THC.

Dependency and Withdrawal According to historical and modern case reports cannabis is a good remedy to combat withdrawal in dependency on benzodiazepines, opiates and alcohol. For this reason, some have referred to it as a gateway drug back. In this context, both the reduction of physical withdrawal symptoms and stress connected with discontinuance of drug abuse may play a role in its observed benefits.

Psychiatric Symptoms An improvement of mood in reactive depression has been observed in several clinical studies with THC. There are additional case reports claiming benefit of cannabinoids in other psychiatric symptoms and diseases, such as sleep disorders, anxiety disorders, bipolar disorders, and dysthymia. Various authors have expressed different viewpoints concerning psychiatric syndromes and cannabis. While some emphasize the problems caused by cannabis, others promote the therapeutic possibilities. Quite possibly cannabis products may be either beneficial or harmful, depending on the particular case. The attending physician and the patient should be open to a critical examination of the topic, and a frankness to both possibilities.

Autoimmune Diseases and Inflammation In a number of painful syndromes secondary to inflammatory processes (e.g. ulcerative colitis, arthritis), cannabis products may act not only as analgesics but also demonstrate anti-inflammatory potential. For example, some patients employing cannabis report a decrease in their need for steroidal and nonsteroidal anti-inflammatory drugs. Moreover, there are some reports of positive effects of cannabis self-medication in allergic conditions. It is as yet unclear whether cannabis products may have relevant effects on causative processes of autoimmune diseases.

Miscellaneous, Mixed Syndromes There are a number of positive patient reports on medical conditions that cannot be easily assigned to the above categories, such as pruritus, hiccup, ADS (attention deficit syndrome), high blood pressure, tinnitus, chronic fatigue syndrome, restless leg syndrome, and others. Several hundred possible indications for cannabis and THC have been described by different authors. Cannabis products often show very good effects in diseases with multiple symptoms that encompassed within the spectrum of THC effects, for example, in painful conditions that have an inflammatory origin (e.g., arthritis), or are accompanied by increased muscle tone (e.g., menstrual cramps, spinal cord injury), or in diseases with nausea and anorexia accompanied by pain, anxiety and depression, respectively (e.g. AIDS, cancer, hepatitis C).

Medical marijuana - ailments/cannabinoids

- Relieves Pain - Analgesic - (THC, CBD, CBN, CBC, CBGa)
- Suppresses appetite / Helps with weight loss - Anorectic - (THCv)
- Kills or slows bacteria growth - Antibacterial - (CBD, CBG, CBCa)

- Reduces blood sugar levels - Anti-diabetic - (CBD)
- Reduces vomiting and nausea - Anti-emetic - (THC, CBD)
- Reduced seizures and convulsion - Anti-epileptic - (CBD, THCv)
- Treats fungal infection - Antifungal - (CBCa)
- Reduces inflammation - Anti-inflammatory - (CBD, CBG, CBC, CBGa, CGCa, THCa, CBDa)
- Aids Sleep - Anti-insomnia - (CBN)
- Reduces risk of artery blockage - Anti-ischemic - (CBD)
- Inhibits cell growth in tumors/cancer cells - Anti-proliferative - (CBD, CBG, CBC, THCa, CBDa)
- Treats psoriasis - Anti-psioratic - (CBD)
- Tranquilizing, used to manage psychosis - Antipsychotic - (CBD)
- Suppresses muscle spasms - Antispasmodic - (THC, CBD, CBC, THCa)
- Relieves Anxiety - Anxiolitic - (CBD)
- Stimulates appetite - Appetite Stimulant - (THC)
- Promotes bone growth - Bone Stimulant - (CBD, CBG, CBC, THCa)
- Reduces function in the immune system - Immunosuppresive - (CBD)
- Reduces contractions in the small intestines - Intestinal Anti-prokinetic - (CBD)
- Protects nervous system degeneration - Neuroprotective - (CBD)

15 Fascinating Facts About Hemp

Hemp is the earth's most persecuted commodity. Hemp can grow without pesticides. The crop also kills some weeds, purifies soil, and is suitable for rotation use due to its short harvest cycle (120 days). Hemp is also a high-yield crop. One acre of hemp produces twice as much oil as one acre of peanuts, and nearly four times as much fiber pulp (for paper) as an acre of trees." Hemp is a sustainable and renewable resource affecting almost every major industry. However, due to decades of propaganda and misinformation, hemp has not received the attention it deserves.

Hemp is the common name for plants of the entire genus Cannabis, although the term is often used to refer only to Cannabis strains cultivated for industrial (non-drug) use. Industrial hemp has many uses, including paper, textiles, biodegradable plastics, construction, health food, and fuel. It is one of the fastest growing biomasses known, and one of the earliest domesticated plants known. Here are 15 fascinating facts about the less-pleasurable version of weed. [Source]

1. All schoolbooks were made from hemp or flax paper until the 1880s. (Jack Frazier. Hemp Paper Reconsidered. 1974.)
2. It was legal to pay taxes with hemp in America from 1631 until the early 1800s. (LA Times. Aug. 12, 1981.)
3. Refusing to grow hemp in America during the 17th and 18th centuries was against the law! You could be jailed in Virginia for refusing to grow hemp from 1763 to 1769 (G. M. Herdon. Hemp in Colonial Virginia).
4. George Washington, Thomas Jefferson and other founding fathers grew hemp. (Washington and Jefferson Diaries. Jefferson smuggled hemp seeds from China to France then to America.)
5. Benjamin Franklin owned one of the first paper mills in America, and it processed hemp. Also, the War of 1812 was fought over hemp. Napoleon wanted to cut off Moscow's export to England. (Jack Herer. Emperor Wears No Clothes.)
6. For thousands of years, 90% of all ships' sails and rope were made from hemp. The word 'canvas' comes from the Middle English word "canevas" which comes from the Latin word cannabis. (Webster's New World Dictionary.)
7. 80% of all textiles, fabrics, clothes, linen, drapes, bed sheets, etc., were made from hemp until the 1820s, with the introduction of the cotton gin.

8. The first Bibles, maps, charts, Betsy Ross's flag, the first drafts of the Declaration of Independence and the Constitution were made from hemp. (U.S. Government Archives.)
9. The first crop grown in many states was hemp. 1850 was a peak year for Kentucky producing 40,000 tons. Hemp was the largest cash crop until the 20th century. (State Archives.)
10. Oldest known records of hemp farming go back 5000 years in China, although hemp industrialization probably goes back to ancient Egypt.
11. Rembrandt's, Van Gogh's, Gainsborough's, as well as most early canvas paintings, were principally painted on hemp linen.
12. In 1916, the U.S. Government predicted that by the 1940s all paper would come from hemp and that no more trees need to be cut down. Government studies report that 1 acre of hemp equals 4.1 acres of trees. Plans were in the works to implement such programs. (U.S. Department of Agriculture Archives.)
13. Quality paints and varnishes were made from hemp seed oil until 1937. 58,000 tons of hemp seeds were used in America for paint products in 1935. (Sherman Williams Paint Co. testimony before the U.S.Congress against the 1937 Marijuana Tax Act.)
14. Henry Ford's first Model-T was built to run on hemp gasoline and the car itself was constructed from hemp! On his large estate, Ford was photographed among his hemp fields. The car, 'grown from the soil,' had hemp plastic panels whose impact strength was 10 times stronger than steel. (Popular Mechanics, 1941.)
15. In 1938, hemp was called 'Billion Dollar Crop.' It was the first time a cash crop had a business potential to exceed a billion dollars. (Popular Mechanics, Feb. 1938.)

As many as 50,000 different things can be made out of hemp. The world's resources are limited and dwindling every day that goes by. We all have a responsibility to better utilize the versatile plant that is hemp, and let it help heal the world. One way we can do this is by replacing products made out of paper or petrochemicals with ones made of hemp. If you're hip to this idea, here are 12 things (out of an estimated 50,000 things!) that should absolutely be made from hemp for the sake of our world.

1. Diapers It is estimated as many as 27.4 billion (that's with a B) disposable diapers are consumed in America alone in one year. All of those end up in landfills, where they take a very long time to decompose since many of them are made out of petrochemicals. There are great options available: cloth diapers can be made from hemp, and don't end up in landfills at nearly the same rate as disposable diapers, and disposable diapers can be made from hemp too.
2. Tampons I am obviously a male, so I will tread lightly on this subject, as I don't have any personal experience with tampons. However, I can point to some math I think will highlight the need to make more tampons out of hemp versus other things. Estimates are that the average woman will go through 9,600 tampons in her lifetime. Multiply that by how many women there are on the planet, consider that many of those products end up in landfills, and it becomes obvious that making tampons out of hemp versus other things that decompose much slower is a good idea.
3. Gloves Hemp plastic doesn't pose the health and safety risks associated with other plastic materials. My friend Chris from Oregon Hemp Works pointed this one out to me. Over 100 billion petrochemical gloves are thrown away each year. Think about it - mechanics, doctors, tattoo artists, janitors, etc., all use disposable gloves as part of their jobs. Imagine if all of those gloves were made out of hemp?
4. Fuel s Rachel Garland pointed out in her earlier article for Green Flower, hemp is the most cost efficient and environmentally friendly fuel crop out there. Hemp can produce two different types of fuel – hemp biodiesel and hemp ethanol/methanol. I once heard a story told by Willy Nelson that he once drove a car to a hemp rally that was powered by hemp biodiesel.
5. Plastic bottles and bags Americans throw away 35 billion plastic bottles every year. A lot of those end up

in landfills, but a lot of them also end up in oceans. The same goes for plastic bags. If you want to feel alarmed, just Google 'Pacific Ocean Garbage Patch.' All of that plastic is going to take a very long time to decompose. If those products were made from hemp, they would have likely already decomposed by now.

6. Houses The components of hempcrete, including hemp hurds, water, and lime binder, form to create a naturally flame resistant building material. The economy is doing well right now, and whenever that happens, homes get built in large numbers. A lot of those houses are built using wood. Why not save those trees and make the homes out of hemp? Homes that are built using hempcrete (building material made from hemp) are more durable than houses built out of wood, and actually have a negative carbon footprint. Houses built out of hempcrete are also more fire resistant.
7. Electronic device casings Look around you; chances are electronic devices surround you with casings made out of plastic made from petrochemicals. Your laptop, tablet, phone, TV, DVD player, etc., all of it is likely made out of petrochemicals. Think about how many of those types of items you have thrown away which are now sitting in a landfill. It's a problem that grows daily.
8. Batteries Rachel Garland pointed out in her earlier Green Flower article. I can't hammer home the points she made enough, as it's estimated that as much as 180,000 tons worth of batteries are thrown away each year. Batteries can be particularly toxic. The reduction in environmental impact alone makes making batteries out of hemp worth it. And, batteries made from hemp can be made at 1/1000 of the cost of our current energy systems and will outperform current energy storing technologies.
9. All clothing Did you know Levi jeans were originally made from hemp sailcloth (and rivets)? Clothing made from hemp is stronger than clothing made from other fibers. But, here's something interesting to know, fiber made from hemp can actually stop the spread of some bacteria. This isn't true for cotton.
10. Furniture Anything wood can do hemp can usually do too. A lot of wood goes into making furniture. People throw away furniture more often than they realize. Couches, chairs, etc. can all be made, top to bottom, out of hemp.
11. Make up and make up containers in not so shocking news, I do not wear makeup and I have never purchased a makeup product. However, there are many, many people out there that do. The makeup itself is not as big an environmental problem, as is the packaging, which is oftentimes excessive, and once opened, it is thrown away. The packaging is almost always made out of wood paper products (the box) and petrochemicals (the plastic holder). All of it can be made from hemp to help reduce the impact on our environment. Plus, my wife tells me, hemp makeup is quality!
12. All paper products Naturally acid-free hemp paper does not yellow as quickly as tree pulp-based paper. Some of the most common things filling up landfills are paper products made from wood; paper towels, toilet paper, bags, newspapers, etc. All of them could be made from hemp, and while wood paper products decompose faster than plastic, they still take a lot of wood to make, which takes a long time to grow. Hemp grows much, much faster. And, hemp paper is stronger than wood-based paper, and can withstand more folding and wear and tear. Hemp is the strongest natural fiber of any source available.

Bible verses related to Cannabis

If cannabis was one of the main ingredients of the ancient anointing oil _ and receiving this oil is what made Jesus the Christ and his followers Christians, then persecuting those who use cannabis could be considered anti-Christ.

The word for cannabis is kaneh-bosm, also rendered in traditional Hebrew as kaneh or kannabus, and appears several times throughout the Old Testament. The first mention of kaneh-bosm in the Old Testament appears with the prophetshaman Moses. This word appears five times in the Old Testament; in the books of Exodus, the

Song of Songs, Isaiah, Jeremiah, and Ezekiel. The sacred character of hemp in biblical times is evident from Exodus 30:22-25, where Moses was instructed by God to anoint the meeting tent and all its furnishings with specially prepared oil, containing hemp. Exodus 30:22-25 - Then the lord said to moses, “take the following fine spices: 500 shekels of liquid myrrh, half as much of fragrant cinnamon, 250 shekels of kannabosm, 500 shekels of cassia – all according to the sanctuary shekel – and a hind of olive oil. Make these into a sacred anointing oil, a fragrant blend, the work of a perfumer. It will be the sacred anointing oil.

Genesis 1:29 – And God said, Behold, I have given you every herb bearing seed, which [is] upon the face of all the earth, and every tree, in the which [is] the fruit of a tree yielding seed; to you it shall be for meat.

Genesis 9:3 – Every moving thing that liveth shall be meat for you; even as the green herb have I given you all things.

Genesis 1:29-31 – And God said, Behold, I have given you every herb bearing seed, which [is] upon the face of all the earth, and every tree, in the which [is] the fruit of a tree yielding seed; to you it shall be for meat.

Genesis 1:12 – And the earth brought forth grass, [and] herb yielding seed after his kind, and the tree yielding fruit, whose seed [was] in itself, after his kind: and God saw that [it was] good.

Anointing was common among kings of Israel. It was the sign and symbol of royalty. The word 'Messiah' signifies the 'Anointed One', and none of the kings of Israel were styled the Messiah unless anointed. After the fall of the Jewish kingdoms, and the bloody purges following the forged discovery of the Book of the Law (1 Kings 23), the cannabis holy oil was prohibited as associated with pagan worship. Yet it seems that certain sects retained the topical entheogen, and continued to practice the older religion, silently awaiting the return of a Messiah-king in the line of David.

The ministry of Jesus marked the return of the Jewish Messiah-kings, and thus the re-emergence of the holy oil. Jesus was called the Christ because he violated the Old Testament taboo on the cannabis oil and distributed it freely for initiation rites and to heal the sick and wounded.

Cannabis use is associated with a substantial reduction in premature deaths in the United States.

Author: Thomas M. Clark, tclark2@iusb.edu Affiliation: Professor and Chair, Department of Biology - Indiana University Date: 2017-08-11 Abstract

Background: Adverse effects of moderate Cannabis use on physical health are subtle and rarely fatal, while Cannabis use is associated with decreased rates of obesity, diabetes mellitus, mortality from traumatic brain injury, use of alcohol and prescription drugs, driving fatalities, and opioid overdose deaths. These data suggest that Cannabis use may decrease premature deaths. To date, no studies have attempted to estimate impacts of Cannabis use on premature death that include both adverse and beneficial effects on physical health.

Results: Marijuana use is estimated to reduce premature deaths from diabetes mellitus, cancer, and traumatic brain injury by 989 to 2,511 deaths for each 1% of the population using Cannabis. Using a monthly user rate of 12.2% in the analysis, this results in an estimated 12,100 to 30,600 deaths from these causes prevented annually due to marijuana consumption. Including MMJ, Cannabis use appears to prevent approximately 17,400 to 38,500 premature deaths annually under current policies. The analysis predicts an estimated 23,500 to 47,500 deaths prevented annually if medical marijuana were legal nationwide. A number of other potential causes of reduced mortality due to Cannabis use were revealed but were excluded from the analysis because quantitative data were lacking. These estimates thus substantially underestimate the actual impact of Cannabis use on premature death. Including states with legal access as of 2015, prohibition is responsible for an estimated minimum of 6,100 to 9,000 deaths annually due to lack of access to medical marijuana, in addition to the increased deaths from cancer, diabetes mellitus, and TBI arising from a decrease in the numbers of people using marijuana. Overall, prohibition is estimated to lead to similar numbers of premature deaths as drunk driving, homicide, or fatal opioid overdose.

Conclusions: Cannabis use prevents thousands of premature deaths each year, and Cannabis prohibition is revealed as a major cause of premature death in the U.S.

Cannabis oil treating Epilepsy, 173 years ago

William Brooke O'Shaughnessy

Everyday I read articles about scientific breakthroughs concerning the medical properties of cannabis, this morning I read an article on how CBD is "a wonder medicine for pediatric epilepsy' and how Amylea Nunez, aged two months was the youngest patient to be prescribed cannabis oil. However, she is not the youngest and cannabis oil as a treatment in paediatric epilepsy is not a new discovery, it is merely a rediscovery.
You can read little Amylea's amazing story: Infant Overcomes Seizures After Becoming Youngest Patient to Take Cannabis Oil

In 1840, Victorian Doctors were treating people with extracts of cannabis for many illnesses, including tinctures for treating children with epilepsy.
One of my favourite pioneers was Dr William Brooke O'Shaughnessy MD, an Irish physician, surgeon, Professor of chemistry, scientist and innovator, he was a pioneer of 'intravenous therapy' and he is the man credited with introducing cannabis to Western medicine.
O'Shaughnessy graduated in 1829 with a Medical Doctorate from the University of Edinburgh. In 1831, at the young age of 22, he investigated cholera and his early work led to the development of intravenous fluid and electrolyte-replacement therapy.
In 1833, O'Shaughnessy moved to Calcutta, India to work for the British East India Company and during his time there he developed new cannabinoid extraction techniques which he used is preparations to treat patients suffering from, cholera, tetanus, analgesia, rheumatism and epilepsy in infants.
In India, he initially studied botanical pharmacology and chemistry, publishing his first paper on medical cannabis in 1839.
In his paper "On the preparations of the Indian hemp, or Gunjah" published in the Provincial Medical Journal, London on February 4th, 1843, O'Shaughnessey relates the case of a baby just over a month old who he administered an ethanol (alcohol) cannabis based tincture.
Please remember this was written 173 years ago.
Case of Infantile Convulsions, 1843
"A very interesting case of this disease has recently occurred in my private practice, the particulars of which I have the permission of the family to insert in this paper. A female infant, forty days old, the child of Mr. and Mrs. J. L., of Calcutta, on the 10th of September had a slight attack of convulsions, which recurred chiefly at night for about a fortnight, and for which the usual purgatives-warm baths and a few doses of calomel and chalk-were given without effect. On that day the attacks were almost unceasing, and amounted to regular tetanic paroxysms. The child had, moreover, completely lost appetite and was emaciating rapidly"
"I had by this time exhausted all the usual methods of treatment, and the child was apparently in a binking state. Under these circumstances I stated to the parents the results of the experiments I had made with the hemp, and my conviction that it would relieve their infant if relief could possibly be obtained. They gladly consented to the trial, and a single drop of the spirituous tincture, equal to the one-twentieth part of a grain in weight, was placed on the child's tongue at 10pm."
1/20th of a grain is 3.24mgs
"No immediate effect was perceptible, and in an hour and a half two drops more were given. The infant fell asleep in a few minutes, and slept soundly till 4pm, when she awoke, screamed for food, took the breast free!y, and fell asleep again. At 9am, 1st of October, I found the child fast asleep, but easily roused; the pulse, countenance, and skin perfectly natural. In this drowsy state she continued for four days totally free from convulsive symptoms in any form.
"During this time the bowels were frequently spontaneously relieved, and the appetite returned to the natural degree. October 4th, At 1am, convulsions returned and continued at intervals during the day; 5 drop doses of the tincture were given hourly. Up to midnight there were 30 fits, and 44 drops of the tincture of hemp were ineffectually given."

"Paroxysms continued during the night. At 11am, it was found that the tincture in use during the preceding days had been kept by the servant in a small bottle with a paper stopper, the spirit had evaporated and the whole of the resin had settled on the sides of the phial. The infant had in fact been taking drops of mere water during the preceding day."

Always shake cannabis preparations before use and store in the fridge.

"A new preparation was given in 3 drop doses during the 5th and 6th, and increased to 8 drops with the effect of diminishing the violence, though not of preventing the return of the paroxysm. On the 7th I met Dr. Nicholson in consultation, and despairing of a cure from the hemp, it was agreed to intermit its use, to apply a mustard poultice to the epigastrium, and to give a dose of castor oil and turpentine."

"The child, however, rapidly became worse, and at 2pm, a tetanic spasm set in, which lasted without intermission till 6.30pm. A cold bath was tried without solution of the spasm; the hemp was, therefore, again resorted to, and a dose of 30 drops, equal to one and a-half grains of the resin, given at once."

Approx: 100mgs

"Immediately after this dose was given the limbs relaxed, the little patient fell fast asleep, and so continued for 13 hours. While asleep, she was evidently under the peculiar influence of the drug. On the 8th October, at 4am, there was a severe fit, and from this hour to 10pm, 25 fits occurred, and 130 drops of the tincture were given in 30 drop doses"

Dr O'Shaughnessy (quite correctly) increased the dose

"It was now manifestly a struggle between the disease and the remedy; but at 10pm, she was again narcotised, and from that hour no fit returned"

"The child is now 17/12/1842 in the enjoyment of robust health, and has regained her natural plump and happy appearance. In reviewing this case several very remarkable circumstances present themselves. At first we find 3 drops, causing profound narcotism, subsequently we find 130 drops daily required to produce the same effect"

He was learning about how tolerance builds, hence the requirement to increase the dose (slowly).

"Should the disease ever recur, it will be a matter of much interest to notice the quantity of the tincture requisite to afford relief. The reader will remember that this infant was but 60 days old when 130 drops were given in one day, of the same preparation of which ten drops had intoxicated the student Dinonath Dhur, who took the drug for experiment"

Dr O'Shaughnessy concludes:

"The preceding cases constitute an abstract of my experience on this subject, and constitute the grounds of my belief that in hemp the profession has gained an anti-convulsive remedy of the greatest value"

The Doctor explains how he prepares his preparations

"The resinous extract is prepared by boiling the rich, adhesive tops of the dried gunjah, in spirit, until all the resin is dissolved. The tincture thus obtained is evaporated to dryness by distillation, or in a vessel placed over a pot of boiling water. The extract softens at a gentle heat, and can be made into pills without any addition"

The alcohol he used was 84.5% ethanol, he was preparing what many people today would refer to as a FECO extraction (full extract cannabis oil).

"Doses, etc.-In tetanus a drachm of the tincture is every half hour until the paroxysms cease, or catalepsy is induced"

A drachm is 1.77 grams and tetanus is also referred to as lockjaw

"In hydrophobia I would recommend the resin in soft pills, to the extent of 10 to 20 grains to be chewed by the patient, and repeated according to the effect"

10 to 20 grains is 0.65 grams to 1.3 grams, and from Dr O'Shaughnessy's description of the pill making process it is actually cannabis oil as we now know it, 1.3 grams is a very significant dose. Hydrophobia is a common symptom of Rabies.

"With the alcoholic extract made from the tops in the way I recommend the practitioner has only to feel his way, and increase the dose until he produces intoxication as the test of the remedy having taken effect"

"Of all powerful narcotics ***it is the safest to use with boldness and decision"***

Cannabis use is associated with a substantial reduction in premature deaths in the United States.

Author: Thomas M. Clark, tclark2@iusb.edu
Affiliation: Professor and Chair, Department of Biology, Indiana University South Bend, 1700 Mishawaka Ave. South Bend IN 46634-1700

Abstract

Background: Adverse effects of moderate *Cannabis* use on physical health are subtle and rarely fatal, while *Cannabis* use is associated with decreased rates of obesity, diabetes mellitus, mortality from traumatic brain injury, use of alcohol and prescription drugs, driving fatalities, and opioid overdose deaths. These data suggest that *Cannabis* use may decrease premature deaths. To date, no studies have attempted to estimate impacts of Cannabis use on premature death that include both adverse and beneficial effects on physical health.

Methods: A systematic review, meta-analysis, and narrative summary of effects of *Cannabis* use on mortality are performed. Studies addressing the impact of *Cannabis* use on physiological systems and metabolism, and fatality rates following brain injury, are used with reported numbers of deaths from these causes and the proportion of the population using *Cannabis* to obtain an initial estimate of the effects of *Cannabis* use on premature death. Changes in death rates and alcohol consumption following legalization of medical marijuana are used with census data from states with legal access to estimate the impact of legalization of medical marijuana.

Results: Marijuana use is estimated to reduce premature deaths from diabetes mellitus, cancer, and traumatic brain injury by 989 to 2,511 deaths for each 1% of the population using *Cannabis*. Using a monthly user rate of 12.2% in the analysis, this results in an estimated 12,100 to 30,600 deaths from these causes prevented annually due to marijuana consumption. Including MMJ, *Cannabis* use appears to prevent approximately 17,400 to 38,500 premature deaths annually under current policiesh. The analysis predicts an estimated 23,500 to 47,500 deaths prevented annually if medical marijuana were legal nationwide. A number of other potential causes of reduced mortality due to *Cannabis* use were revealed, but were excluded from the analysis because quantitative data were lacking. These estimates thus substantially underestimate the actual impact of *Cannabis* use on premature death. Including states with legal access as of 2015,

prohibition is responsible for an estimated minimum of 6,100 to 9,000 deaths annually due to lack of access to medical marijuana, in addition to the increased deaths from cancer, diabetes mellitus, and TBI arising from a decrease in the numbers of people using marijuana. Overall, prohibition is estimated to lead to similar numbers of premature deaths as drunk driving, homicide, or fatal opioid overdose.

Conclusions: *Cannabis* use prevents thousands of premature deaths each year, and *Cannabis* prohibition is revealed as a major cause of premature death in the U.S.

Introduction:

There is growing acknowledgement of the medical and therapeutic benefits of the unique pharmacologically active compounds produced by *Cannabis* (marijuana). These compounds, known collectively as cannabinoids, include Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) that act on the endocannabinoid system of vertebrates and other animals [1]. Millions of people find relief from a variety of medical conditions including chronic and neuropathic pain, neurodegenerative and neuroinflammatory diseases, inflammation, and nausea and emesis using *Cannabis* [2-9]. In recent surveys of medical marijuana patients, eighty percent of patients report reduced use of prescription drugs upon initiation of medical marijuana, citing more effective relief of symptoms, less withdrawal, and fewer adverse side effects as reasons for the switch [10,11]. Prescriptions for drugs used to treat pain, anxiety, nausea, psychoses, seizures, sleep disorders, depression, and spasticity decrease following legalization of medical marijuana [12]. Decreases are also reported in use of illicit drugs and alcohol by medical marijuana (MMJ) patients [10,11,13].

Recent reviews have addressed the adverse effects of *Cannabis* [14-17], and several have attempted to estimate the impact of *Cannabis* on the global burden of disease or the number of deaths caused by *Cannabis* use [18-21]. It is clear that heavy use of *Cannabis* has deleterious effects on health. However, these recent analyses only include deleterious effects of *Cannabis* use. Recent studies documenting potentially beneficial effects of *Cannabis* use on health are ignored. It is the net effect on health and mortality, including both adverse and beneficial effects, that is most important for public health - if only deleterious effects were considered, then water, food, and exercise would all be considered harmful. Furthermore, it should be obvious that non-fatal detrimental effects such as *Cannabis* use disorder are less important than effects on premature

death. While use disorders can have significant negative impacts on quality of life, one can recover from use disorders. Premature death, on the other hand, is final.

Evidence for harmful effects leading to a net increase in mortality due to *Cannabis* use is weak. A number of recent studies have found no increase in the mortality rate of *Cannabis* users. One study followed a cohort of users from age 18 to 38, and found that the only negative health outcome in the end of this period arising from *Cannabis* consumption was periodontal disease, while some health outcomes (HDL, cholesterol, triglyceride, and glycated Hb levels) were improved in users [22]. The failure to detect an association between *Cannabis* use and poor physical health in midlife was not due to better initial health, or healthier lifestyles in *Cannabis* users counteracting harmful effects of *Cannabis* use, but rather arose from an absence of any significant effect of *Cannabis* use (Meier et al. 2016) [22]. A study following adolescent users into their mid-thirties did not find any association of even heavy marijuana use with health problems [23]. Another longitudinal study found no increase in mortality over fifteen years, after adjustment for social background variables, in a group of over 45,000 Swedish military conscripts [24]. Fuster et al. [25] found that daily *Cannabis* use was not associated with increased emergency hospital visits (aOR 0.67, 95% CI 0.36 – 1.24), or rates of healthcare utilization, among patients reporting use [25]. Sidney et al. found that, after accounting for increased rates of *Cannabis* use in AIDS patients, marijuana use was not associated with increased mortality [26]. One study from Switzerland even detected a dose dependent and significant decrease in the risk of injury with *Cannabis* use (OR = 0.33, 95% CI .12 - .92) [27]. There is thus little or no support for the hypothesis that moderate marijuana use leads to significant health problems, or increased mortality rates, even following years of use.

While evidence is not consistent with moderate *Cannabis* use leading to fatal outcomes, even after years of use, there is emerging evidence suggesting that moderate *Cannabis* use may lead to significant positive health outcomes. A number of recent studies have shown lower rates of obesity, or healthier BMI, in current *Cannabis* users, effects that remain after full adjustment of the data for confounding factors [22,28-30]. The United States is in the midst of an obesity epidemic, and obesity is positively correlated with increased rates of a number of significant health issues, including cancer, cardiovascular disease, chronic kidney disease, diabetes mellitus, and Alzheimer's disease [31,32]. These obesity-related diseases have a huge impact on public health. Given that extensive research has shown that deleterious effects on physical health are subtle, and

generally are not fatal, this leads to the prediction that inclusion of beneficial effects in estimates of the public health impact of *Cannabis* use will reveal that *Cannabis* use decreases the premature death rate. The present systematic review and meta-analysis attempts to provide an initial, rough estimate of the overall effects of *Cannabis* use on the mortality rate that includes evidence for both beneficial and deleterious effects.

Rationale: Recent studies have attempted to estimate the harm caused by *Cannabis* use from its effects on mortality and burden of disease. These studies are biased as they only consider deleterious effects and ignore substantial evidence for beneficial effects of moderate *Cannabis* use through effects on obesity rates and oxidative damage. The data available at this time thus suggest that the net impact of *Cannabis* use on public health, at least in terms of premature death, may be beneficial. Analyses considering both harmful and beneficial effects of *Cannabis* use in estimates of the net impact on public health are needed.

Objectives: The current study has four main objectives. These are:

1. Identify in the literature quantitative data on causes of death influenced by *Cannabis* use.
2. Determine whether available evidence on the impact of *Cannabis* use on physical health is consistent with a net beneficial or harmful impact on public health.
3. Provide an initial, rough estimate the magnitude of the effects of *Cannabis* use on the rate of premature deaths in the U.S.
4. Provide a supporting framework to assist interpretation of the results.

Methods:

Systematic review of the literature on the influence of *Cannabis* use on mortality:

This research did not involve human subjects as it is a systematic review analyzing published data. The study was performed as a systematic review with meta-analysis and narrative synthesis following PRISMA protocols [33].

Review protocol: The effects of *Cannabis* use on mortality from effects on organ systems and disease states considered most likely to be influenced by *Cannabis* were investigated. These were cancer, appetite and metabolism, cardiovascular disease, liver disease, lung disease, and brain injury. Then, data on changes in mortality rates or harmful behaviors following legalization of medical marijuana were sought and analyzed. The search engines Google Scholar and PubMed were used to identify relevant papers on these topics. The initial screen of the articles emerging from these searches selected papers reporting odds ratios or equivalent measures comparing

rates of disease states in users and non-users, survival rates of users and non-users, or changes in fatalities following changes in legal status. Additional articles were sought in the reference sections of primary and review papers identified in this initial search. These studies were subjected to further analysis and supplemented with qualitative evidence allowing context. A second round of targeted searches was then performed for articles that illuminated issues arising in the initial search. The screen was performed twice, most recently in August 2016.

Eligibility criteria: Studies published since 2000, that addressed the impact of marijuana on potentially fatal diseases, survival of accidents and accident rates, or the effects of legalization of medical marijuana on mortality, were sought. Relevant studies were in English. Studies included in the quantitative analysis must report quantitative data comparing the incidence of diseases, such as rates of cancer, diabetes mellitus, cardiovascular disease, liver disease, or lung disease, in *Cannabis* users and non-users. To be included into the meta- analysis, studies must adjust for tobacco use and other confounding factors, and provide data for usage typical of the US population.

Information sources: Google Scholar, PUBMED, and reference sections of identified research and review articles were screened for relevant papers.

Search: The initial search for articles on the correlation between cancer rates and *Cannabis* use was performed using search terms "*Cannabis* and cancer" and 'marijuana and cancer'. Search terms used for diabetes mellitus were "*Cannabis* and diabetes mellitus" and 'marijuana and diabetes mellitus". Search terms for traumatic brain injuries were "*Cannabis* and brain injury" and 'marijuana and brain injury'. Search terms for cardiovascular disease were "*Cannabis* and cardiovascular disease" and "marijuana and cardiovascular disease". Search terms for lung disease were "*Cannabis* and lung disease" and "marijuana and lung disease". Search terms for liver disease were "*Cannabis* and liver disease" and "marijuana and liver disease". For medical marijuana (MMJ), an initial search was performed using the phrases "Medical marijuana and mortality", indicating possible effects on suicides, opioid use and overdose deaths, driving fatalities, and alcohol use. This initial search was followed by searches for "*Cannabis* and suicide" and "marijuana and suicide", "*Cannabis* and opioid or opiate overdose" and "marijuana and opioid or opiate overdose", "*Cannabis* and driving fatalities" and "marijuana and driving fatalities", and "*Cannabis* and alcohol use" and "marijuana and alcohol use", respectively.

Data collection process: Citations appearing in database searches were copied into word and endnote files by search topic: i.e. *Cannabis* and cancer, *Cannabis* and DM, etc., and were initially

screened for relevance by reading the title. Those articles selected in the initial screen were then considered in more detail by reading the abstract, and those providing data relevant to the study were then read in detail. Additional sources identified in reference sections of primary and secondary literature, and results of further searches to illuminate and clarify questions arising during the analysis of mortality data, were included in the analysis.

Data items: Quantitative data for effects of *Cannabis* use on causes of death hypothesized to be influenced by *Cannabis* use were identified. Causes of death investigated included obesity-related diseases such as cancer, diabetes mellitus, cardiovascular disease, and Alzheimer's disease, and diseases associated with exposure to toxins including liver disease and lung disease. Due to the well known neuroprotective effects of cannabinoids, impact of Cannabis use on mortality from traumatic head injury was also investigated. The impact of legalization of medical marijuana on death rates was also investigated.

Potential effects on other causes of death revealed during the search, but for which quantitative data are not available, were included in the qualitative analysis.

Summary measures: The principal summary measure is changes in the rates of diagnoses and premature deaths due to *Cannabis* use, as estimated from published odds ratios or hazard ratios for disease states and TBI, and percentage changes in reported deaths following legalization of medical marijuana.

Calculations to estimate the impact of *Cannabis* use on the mortality rate from impact on physical health:

The search revealed data for cancer, diabetes mellitus, and traumatic brain injury that could be used to estimate the impact of *Cannabis* use on deaths. For cancer and diabetes mellitus, reported odds ratios, relative risk, or hazard ratios comparing users and non-users are used to estimate the effect of *Cannabis* use on the numbers of diagnoses and deaths from cancer and diabetes mellitus. While these are not identical measures, they are similar, represent the best data available, and can be used to provide a preliminary estimate of impact on premature death, revealing at minimum whether the impact is positive or negative and providing a rough estimate of the relative impact. For traumatic brain injury, the odds ratio for mortality of similarly injured patients testing positive and negative for *Cannabis* use are used. Estimates of the effects of *Cannabis* use on the number of fatalities from cancer, diabetes mellitus, and traumatic brain injury

are calculated using Formula 1:

Formula 1: $E = DUR$

In formula 1, E = the change in diagnoses or deaths from a cause due to *Cannabis* use, D = reported annual number of diagnoses or deaths from that cause, R = (1 - the published odds ratio, hazard ratio, or relative risk), and U = the estimated *Cannabis* user rate as a percent of the population. Calculations are made the estimate of 12.2% the proportion of people age 12 and over using *Cannabis* in the previous month, from the National Health and Nutrition Examination Survey, 2007-2010 [34], giving U = 0.122. A positive value for E is the estimated reduction in numbers of diagnoses or deaths from that cause due to use of *Cannabis*, whereas a negative value for E is the estimated increase in diagnoses or deaths as a result of *Cannabis* use.

Statistical methods for analysis of cancer data:

When publications report relative rates of cancer for a variety of different usage patterns, the odds ratio for ever users versus never users (reflecting average or typical use), or for current users vs. non-users, from the fully adjusted model, was used as available. If these were not presented, the mean of the relative rates of cancer across user groups was used (see supplemental excel file). Numbers in 2013 of diagnoses for each cancer type were obtained from the American Cancer Society, and the numbers of deaths are the mean of numbers reported for 2013 by the American Cancer Society and the Centers for Disease Control, which differed slightly [35,36]. The number of deaths from HNSCC, pharyngeal cancer, or oral cancer were not reported in either the CDC or American Cancer Society databases [35,36]. Therefore, the estimate the impact of *Cannabis* use on cancers of the head and neck used the mean OR across undistributed HNSCC, nasal, oral, oropharyngeal, pharyngeal, and laryngeal cancers (mean = 0.83, 95% CI 0.64 – 1.02) with the sum of the numbers of diagnoses and deaths reported for these cancers (55,640 diagnoses and 13,005 deaths) (Table 1, see also supplemental excel file).

Screening of cancer studies:

Studies that presented data on the impact of *Cannabis* use on cancer rates were selected and screened for data quality. Thirty-one such articles were identified through database searches and through other sources (most of these were published prior to the cutoff date of 2000 used in the initial search) [37-68]. Only studies that provided odds ratios or hazard ratios that could be

used to estimate the impact of *Cannabis* use on rates of cancer, that were adjusted for known confounding factors including tobacco or alcohol use or demonstrated no effect of these factors on the cancer in question, were included in the analysis (Supplemental excel file). The studies meeting the selection criteria provided 38 data points (some studies provided odds ratios for multiple cancer types or sites) (Supplemental excel file). An additional 15 studies presented quantitative data but did not meet selection criteria and were removed during screening, as follows: the study by Zhang et al. [38] on lung cancer did not report data for ever vs. never users, or odds ratios that could be averaged across user groups. The study by Zhang et al. [39] reported an odds ratio of 2.6 for HNSCC, well outside the range of the data from other studies of head and neck cancers and HNSCC (mean = 0.83, 95% CI 0.63 – 1.02, N = 17). This was found to be a statistical outlier using the Grubbs test [69] ($P < 0.01$, $G = 2.91 > G_{crit} = 2.821$, $N = 18$, $\bar{Y} = 0.93$, and $s = 0.57$) and was eliminated from the analysis. Efird et al. [41] reported an odds ratio for *Cannabis* use and gliomas, but the study was designed to detect effects of cigarette smoking and included a large proportion of subjects who declined to state whether they used *Cannabis*. Furthermore, multiple laboratory studies have consistently shown that THC and cannabinoids eliminate gliomas in rats and destroy glioma cells *in vitro* with no cytotoxicity for surrounding cells [70,71]. A pilot clinical study in patients with recurrent, treatment resistant glioblastoma showed that THC decreased proliferation of the tumor cells [72], The reported odds ratio for gliomas [40] was therefore excluded from the analysis. Reports on effects of *Cannabis* consumption on cancer rates from studies performed in North Africa were excluded because *Cannabis* is consumed as hashish or kiff with tobacco in North Africa [41-46] and does not represent typical ingestion methods used in the US [47]. These studies consistently show higher rates of lung cancer than studies performed in the US or Europe. Other reports were excluded as follows. One study was rejected because no adjustment was made for tobacco and only the highest usage group was included (average 48 joint years) [45]. Five studies were rejected because no adjustment was made for tobacco use [46,48,51,63,65]. Three were rejected because the study did not report odds ratios nor present data that could be extrapolated to give an estimate of OR [49-51], and one was rejected because data for effects of *Cannabis* use were only reported for HIV positive patients who might be expected to have compromised immune systems [52].

Results:

The systematic search results are presented as a PRISMA diagram (Figure 1). The primary

database searches yielded 3605 articles. An additional 345 articles were identified through other sources. Removal of duplicates yielded a net of 1401 articles that were subjected to further screening. Of these, 898 were excluded and 503 were assessed further. A total of 222 articles were included in the qualitative analysis, and 23 were identified that provided data comparing relative rates of diseases of deaths in users and non-users, that could be used to estimate the impact of *Cannabis* use on the premature death rate. These were as follows: cancer (16), DM (2), TBI (1), driving fatalities (2), OD (1), and alcohol (1).

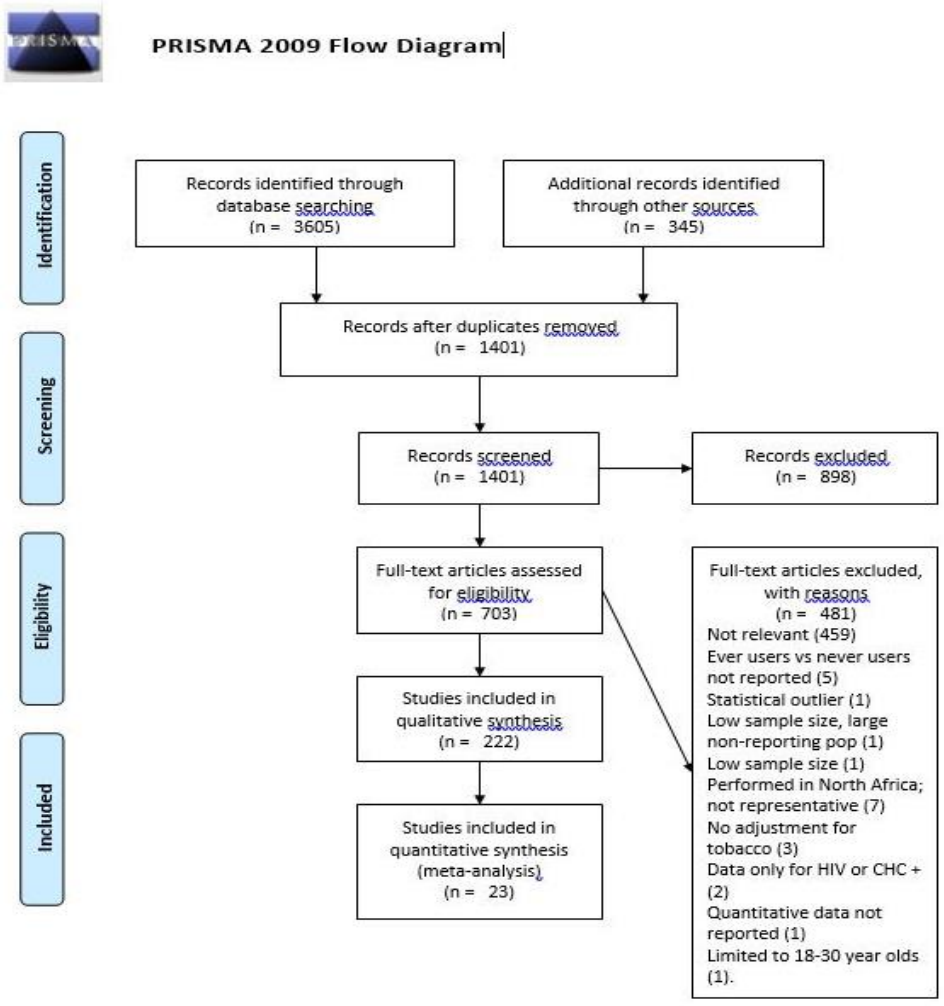

Figure 1: Prisma flow diagram of systematic search.

Effects on BMI and obesity.

Emerging evidence demonstrates critical roles for the endocannabinoid system in appetite, food intake, energy balance, and metabolism [73]. The United States, and much of the developed world, is currently in the midst of an obesity crisis, and obesity is causally associated with a number of significant health problems including diabetes mellitus [31]. Diabetes mellitus (DM) is a leading cause of death worldwide, accounting for an estimated 3.96 million premature deaths (15.7% of all deaths), in the year 2010 [74]. The economic cost in 2007 of DM, in the US alone, was estimated at 174 billion dollars [75].

Evidence strongly supports reduced obesity and diabetes mellitus in people who use *Cannabis*. The most common finding of studies to date have shown lower BMI, waist circumference, or rates of obesity in *Cannabis* users [22,28-30,76]. Le Strat and Le Foll [30] presented data from two epidemiological surveys, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the National Comorbidity Survey – Replication survey (NCS-R). These data sets included 41,654 and 9,106 respondents, respectively. The prevalence of obesity was lower in marijuana users, and the proportion of obese individuals decreased with frequency of marijuana use, in both surveys. These effects remained after adjustment for confounding factors [30]. Rajavashisth et al. [76] reported that marijuana use was associated with a dosage-dependent decrease in the obesity rate, with the most frequent usage (≥ 5 times/month) showing one half the obesity rate of non-users, and the effects on obesity were dose-dependent and remained after adjustment for confounding factors. Ngueta et al. [29] investigated the relative rates of obesity among Inuits, and found a significant decrease in BMI in current *Cannabis* users ($P < 0.001$), who showed 56% the obesity rate of non-users. Meier et al. [22] showed decreased BMI in cannabis users. Because of these observations, Le Foll et al. [77] have proposed therapeutic use of *Cannabis* or THC for weight loss.

Effects on Cancer.

The relationship between *Cannabis* and cancer is complex. Cancer is positively correlated with obesity [31], and obesity decreases in a dose-dependent fashion with *Cannabis* use [28-30], whereas *Cannabis* smoke contains carcinogens. On the other hand, a casual examination of the literature reveals numerous laboratory studies demonstrating that cannabinoids have potent anti-tumoral properties *in vitro* and in mouse models. Cancers inhibited by cannabinoids include

gliomas, thyroid epithelioma, lymphoma, neuroblastoma, and carcinomas of the oral region, lung, skin, uterus, breast, prostate, pancreas, and colon [70-72,79-87]. Thus, *Cannabis* may reduce the risk of getting cancer by reducing obesity rates and by direct inhibition of tumor formation or growth. In addition to these anti-tumor and anti-obesity properties, there is growing interest in the use of *Cannabis* and cannabinoids in palliative cancer care due to their abilities to reduce opioid use and counteract a number of negative effects of chemotherapy [88-90]. Potential palliative effects include suppression of nausea and emesis, bone loss, nephrotoxicity, and cardiotoxicity, as well as improving mood and outlook and providing relief from insomnia [88-90].

Which effect predominates, the carcinogenic properties of the smoke, or the anti-tumor and anti-obesity properties of the cannabinoids? A recent review by Huang et al. [91] noted that some studies investigating the link between *Cannabis* use and cancer report decreased cancer rates in *Cannabis* users, while others report increased rates. Overall, however, they found no significant association between cancer rates and marijuana use. The current systematic review includes a number of data points not included in the study by Huang et al. [91], and screens the reports more aggressively. Furthermore, Huang et al. [91] made no attempt to relate the data for the effects of *Cannabis* use on risk of individual cancer types to the overall impact of *Cannabis* use on premature deaths from cancer. The current study attempts to do so using estimates of the proportion of the population using *Cannabis*, the odds ratios for cancer in users and non-users, and the number of deaths from cancer annually, for each cancer type. Thus, impacts of *Cannabis* use on cancers are weighted to take into account the numbers of diagnoses and deaths from each cancer type as well as the impact of *Cannabis* use, to determine the overall impacts on cancer deaths.

The conclusions reached in the present study for cancers of the head and neck differ from those of the recent meta-analysis of de Carvalho et al. [92], who found no effect of *Cannabis* use on head and neck cancers (grand mean OR 1.02). The current analysis screened the data more carefully (see above). After screening of the data, the current analysis, using reported fully adjusted values from relative rates of cancer types comprising 1,159,120 (70% of total) cancer diagnoses and 355,855 (61% of total) cancer deaths, yields a mean of 0.86, (95% CI = 0.77 - 0.96, N = 34) across all reported values meeting the selection criteria. The grand mean of values for each cancer site yielded a value of 0.89 (95% CI 0.75 – 0.98, N = 15). This estimate is lower than other studies due to a more complete search of the literature and more aggressive screening of the data, as described above. Many studies showed decreases in multiple user groups. The results of

this analysis suggest that moderate *Cannabis* may reduce cancer rates in U.S. users. This effect would be expected to increase if consumers shifted to delivery methods other than smoking, such as edibles or vaping, thus avoiding the carcinogens produced during combustion.

Meta-analysis:

A total of 38 data points representing 15 cancer sites were found to meet the screening requirements and were accepted into the final analysis. Summary of these data points support decreased rates of cancer in *Cannabis* users. Of these 38 data points, 22 (58%) showed a relative rate below 1.0, and only 12 (32%) showed a relative rate of cancer > 1.0 (Fig. 2).

There is clear evidence justifying assumptions of causality for decreased cancer in users, in the abundant laboratory studies showing anti-tumor properties of cannabinoids [70-72,79-87] and in the dosage dependent decrease in BMI or obesity rates of *Cannabis* users [22,28-30,76]. The studies and data included in the cancer meta-analysis are presented in supplemental excel file and Table 1, and in Figure 2.

When numbers of diagnoses and deaths from each cancer type with reported OR are entered into Formula 1 together with the reported OR for that cancer type, and using a user rate of 12.2% in the analysis, the analysis yields a decrease of 5,231 cancer diagnoses and 2,717 deaths each year (Table 1). These numbers for cancers with reported relative rates in users and non-users are used as lower estimates of the impact of *Cannabis* on cancer (Table 1). Odds ratios for *Cannabis* use on rates of a number of cancer types, including pancreatic, kidney, and uterine corpus cancers, are not available, but rates of these cancers are strongly correlated with obesity [93]. Pancreatic, kidney, and uterine cancers cause an additional 162,970 deaths/year (CDC) [35]. Because *Cannabis* users have significantly reduced rates of obesity relative to non-users [22,28-30,76], *Cannabis* is likely to reduce the risk of these cancer types even if it is found to have no direct anti-tumor activity on these cancers. This does not appear to be the case, however, as cannabinoids inhibit *in vitro* cell growth of uterine and pancreatic carcinomas, as well as thyroid epithelioma and neuroblastoma, other cancer types for which odds ratios are not reported [70-72,79-87]. The cannabinoids, with their potent anti-tumor properties, would be distributed throughout the body and thus expected to act on many distinct cancer types, whereas the carcinogens from *Cannabis* smoking would be at highest concentrations in certain organs (oral region, airways, lungs, esophagus) that have been the main targets of investigations of the effects of *Cannabis* on cancer rates. The overall effects of *Cannabis* use on cancer diagnoses and deaths is

therefore likely to be greater than the effects estimated using data on cancers with reported OR. The overall effects of *Cannabis* use on all cancers were therefore extrapolated from cancers with reported OR using the mean reported relative incidences across cancer sites (mean OR = 0.89) and the total numbers of diagnoses and deaths from all cancer types (1,665,540 diagnoses and 585,720 deaths, [35,36]). This extrapolation results in an estimated overall decrease of 22,351 diagnoses and 7,860 deaths at an estimated user rate of 12.2%.

Some of the cancer studies presented data that could be assigned to at least one of the following groups: low use (0-1 joint-year), medium use (1-10 joint-years), and high use (10+ joint-years) (Supplemental excel files). In this subset of the data, the low and medium usage groups show significantly reduced rates of cancer relative to non-users (low usage: OR = 0.76, 95% CI 0.62 – 0.94; N = 22, medium usage: OR = 0.77, 95% CI = 0.63 – 0.92, N = 15). This decrease was not observed in the high usage group (OR = 1.34, 95% CI = 0.83 – 1.85, N = 22) (supplemental excel file; Figure 3). The relationship between *Cannabis* and cancer therefore does not appear to be dose dependent. Note that no usage group showed a significant increase in rates of cancer from *Cannabis* use in this data set.

CANCER TYPE	Total Diagnoses	Total Deaths	Odds ratio (N)	Decrease diagnoses	Decrease deaths
H&N	55,640	13,005	0.83 (17)	1154	270
Esophageal	17,990	14,950	0.61 (1)	856	711
Lung	228,190	157,866	1.02 (5)	-557	-385
Prostate	238,590	28,701	1.3 (1)	-8,732	-1,050
Cervical	12,340	4,024	1.1 (1)	-150	-49
Colorectal	136,830	50,310	0.75 (2)	4,173	1,534
Melanoma	76,100	9,710	1.15 (2)	-1,393	-177
Testicular	7,920	370	1.0 (5)	0	0
Bladder	72,570	15,484	0.55 (1)	3,984	850
Anal	7,060	880	0.8 (1)	172	21
Penile	1,570	310	1.0 (1)	0	0
Breast	234,580	40,678	0.8 (1)	5,724	993
Lower Est.	**1,159,120**	**355,855**	**0.86 (38)**	**5,231**	**2,717**
Upper Est.	**1,665,540**	**585,720**	**0.89 (15)**	**22,352**	**7,860**

Table 1: Summary of effects of *Cannabis* use on cancer diagnoses and deaths, by cancer type.

Effects of *Cannabis* use on mortality rates were calculated using Formula 1 with data in the Supplemental excel files, using an estimated user rate of 12.2%. The numbers of diagnoses and deaths reported for each cancer type in the year 2013 were obtained from the American Cancer Society and the Centers for Disease Control [35,36]. H&N refers to cancers of the head and neck include HNSCC, oral, oropharyngeal, pharyngeal, and laryngeal cancers. NHL refers to non-Hodgkin's lymphoma. Positive values in the columns for reduction in diagnoses or deaths show a decrease, while negative values show increased diagnoses or deaths. **"*Lower Est.*"** shows the result across cancers with reported OR (70% of total cancer diagnoses and 61% of deaths) using the grand mean of the relative rates of cancer in users and non-users across studies, and is used as the lower estimate for effects of *Cannabis* use on cancer rates. **"*Upper Est.*"** is the estimate generated extrapolating the mean of reported relative incidence values by cancer site to all cancers, and is used as the upper estimate of effects of *Cannabis* use on cancer. The references and data used to create this table are presented in the Supplemental excel file.

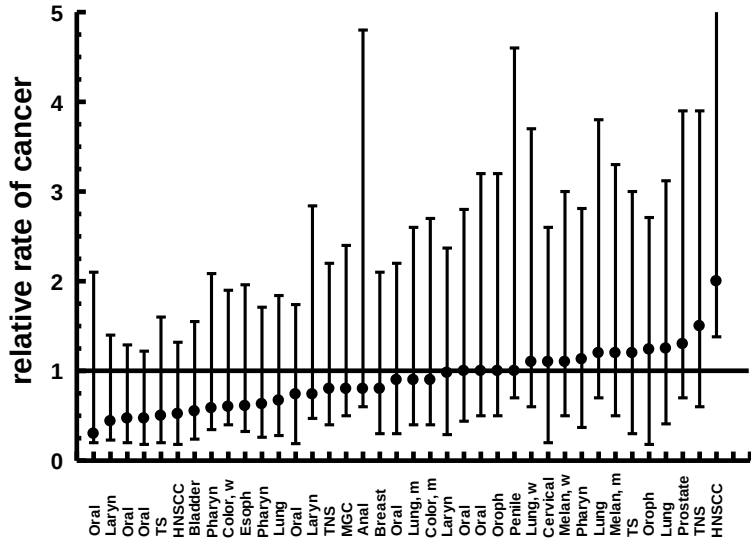

Figure 2: Forest plot of adjusted cancer data. Data are represented as mean ± 95% CI of data reported in the Supplemental excel file. Relative frequency refers to raw data in the form of odds ratios, hazard ratios, and relative risk. HNSCC = head and neck squamous cell carcinoma, Pharyn = pharyngeal, larynx = laryngeal, esoph = esophageal, color = colorectal, melan = melanoma, TS = testicular seminoma, TNS = testicular nonseminoma, N-HL = non-Hodgkins lymphoma, m = men, w = women. Note that only one data set shows significantly higher rates of cancer in *Cannabis* users, and that nearly twice as many data sets show relative rates < 1 (N = 22) than > 1 (N = 12). The references and data used to create this figure are presented in the Supplemental excel file.

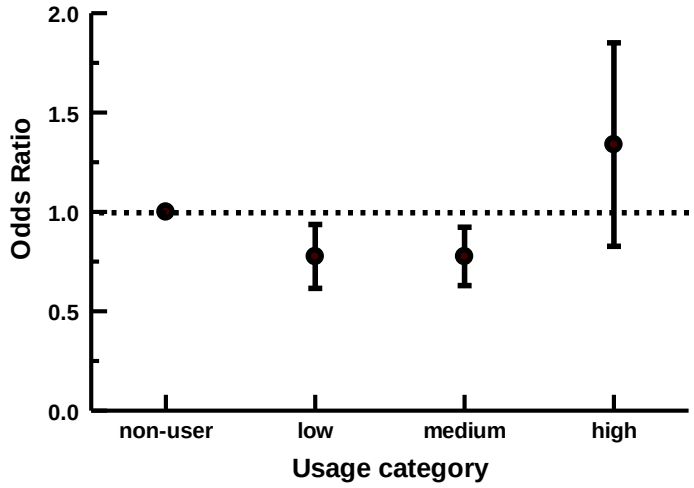

Figure 3: Effects of usage patterns on cancer risk. Some studies (identified in Table 1 with (UR) reported OR for low, medium, and heavy use. Values that could be categorized into low usage (0 – 1 joint-years; N = 22), medium usage (1-10 joint years; N = 15), and high (10+joint years; N = 22) usage rates were pooled. The references and data used to create this figure are presented in the Supplemental excel file.
Data are presented as mean ± 95% CI.

Effects on diabetes mellitus (DM)

Diabetes mellitus (DM) is strongly correlated with BMI and obesity [31], and is also associated with inflammation [94]. Because *Cannabis* use reduces obesity rates, and cannabinoids have potent anti-inflammatory properties, *Cannabis* may decrease rates of DM. Two studies to date in the U.S. have compared rates of DM in *Cannabis* users and non-users, and both detected significantly decreased rates of DM in *Cannabis* users that hold up after adjustment for confounding variables [76,78]. Rajavashisth et al. [76] performed a multivariate model based on the Centers for Disease Control's National Health and Nutrition Examination Survey (NHANES III), using data sets from 1988 to 1994. This study included 10,896 adults, and robust multivariate analysis adjusting for sociodemographic variables, laboratory values, inflammatory marker, and comorbidity showed that *Cannabis* users had a large and significant reduction in rates of DM (fully adjusted OR 0.36, 95% CI 0.24 – 0.55, $P < 0.0001$). This effect was driven primarily by differences in the 41- 59 year old age group. Users also showed reduced LDL and elevated HDL, and reduced serum glucose relative to non-users. Alshaarawy and Anthony [78] then replicated these results,

analyzed yearly surveys from the NHANES and the National Surveys on Drug Use and Health over the years 2005 to 2012, yielding a meta-analytic summary-adjusted OR of 0.7 for DM (95% CI 0.6-0.8) [78]. This analysis also showed that past and present *Cannabis* users had lower serum insulin and measures of insulin resistance than non-users [78]. Ngueta et al. [29] and Penner et al. [95] did not compare relative rates of DM in users and non-users, but both reported reduced fasting insulin and insulin resistance among *Cannabis* users. HIV-HCV patients using *Cannabis* were found to have significantly lower rates of insulin resistance than non-users (OR 0.4) [96]. On the other hand, two smaller and more limited studies [97,98] failed to detect differences in plasma glucose levels between users and non-users. The study by Muniyappa et al. [97] consisted of only 30 users and 30 non-users, and the data were adjusted for BMI. The analysis by Rodondi et al. [98] was limited to young adults aged 18 – 30 years old, a group which did not show decreased rates of DM in the study by Rajavashiseth et al. (OR 0.93) [76].

The correlations between *Cannabis* use, DM, and improved blood lipid and glucose metabolism are supported by laboratory studies in mice. The incidence of DM in non-obese diabetes-prone (NOD) mice was reduced from 86% to 30% with CBD treatment [99,100], and glucose uptake by insulin-resistant adipocytes is increased by exposure to THC *in vitro* [101]. There is thus strong evidence that *Cannabis* use significantly reduces the incidence of DM. Furthermore, cannabidiol is reported to be beneficial in diabetic cardiomyopathy [102], to reduce the endothelial inflammation and retinal damage caused by high blood glucose [103], and *Cannabis sativa* extracts protect against nerve damage in animal models of DM [104]. Thus, in addition to reducing the incidence of DM, *Cannabis* appears to improve outcomes in people who develop DM, as well as improving quality of life by alleviating neuropathic pain [3,105].

Meta-analysis:

Two large studies were identified that presented relative rates of DM in users and non-users, and both show significant decreases in DM in fully adjusted models [76,78]. There is clear evidence justifying the assumption of causality in the relationship between *Cannabis* use and DM, in the form of replicated observational studies showing dose-dependent effects of marijuana use on BMI and obesity, and improved blood glucose and lipid levels and decreased insulin resistance of users [22,28-30,76,78,95,96]. Causation is further supported by studies of experimental models of the disease (i.e. NOD mice and adipocytes, [99-104]. The adjusted odds ratios provided by Rajavashisth et al. [76] and Alshaarawy and Anthony [78] were used in the analysis. In the US,

there are approximately 1,700,000 diagnoses of DM each year [106]. DM was reported as the cause of 75,578 deaths [35], and as a contributing factor in 234,051 deaths in the U.S. [106]. These numbers are similar to the estimate of Roglic et al. [74], of 313,208 deaths from DM in North America in 2010. Deaths from DM are almost certainly underreported [107]. For example, the cardiovascular damage caused by DM is a major cause of death from DM, yet only 39% of diabetes patients dying of cardiovascular disease had DM listed on the death certificate [108].

In the current analysis, assuming that 12.2% of the adult population used *Cannabis* in the last month, *Cannabis* use is estimated to prevent 97,500 DM diagnoses annually. Upper and lower estimates of the impact on mortality suggest that *Cannabis* use prevents 4,300 to 17,800 premature deaths from DM annually (Table 2). The smaller value for each user rate is the estimate based on deaths for which DM was listed as the cause of death, and the larger value is based on total numbers of deaths with DM as cause or contributing factor.

Effects on cardiovascular disease:

Studies to date have failed to detect an effect of *Cannabis* use on atherosclerotic cardiovascular disease, or on cardiovascular health, or on net mortality from cardiovascular problems [28-30,109-111]. Cardiovascular disease is strongly associated with increased BMI and obesity, and both measures are reduced in *Cannabis* users [22,28-30,76]. *Cannabis* use is not correlated with cardiovascular risk factors, including hypertension, atherogenic dyslipidemia, or DM when alcohol and tobacco use are accounted for [76,95,96,111,112]. However, *Cannabis* smoking poses a risk for acute, potentially fatal cardiovascular episodes due to increased blood pressure and vasospasms [113-124] . Many, but not all, of reported cases involve alcohol and/or other drugs [122], and deaths involving only *Cannabis* appear to be rare [114], although mortality is increased in patients who use *Cannabis* following MI [125,126]. However, tolerance to the acute cardiovascular effects develops rapidly [110,122], and over longer periods of use *Cannabis* reduces multiple risk factors for cardiovascular disease including DM and obesity [22,28-30, 76,68]. Furthermore, cannabinoid therapy reduces the progression of atherosclerosis in mice [127] and cannabinoids are potent inhibitors of inflammation [128], a hallmark of atherosclerosis thought to contribute strongly to its harmful effects [129]. Ingestion of cannabinoids (by means other than smoking) has been suggested as a way to reduce the progression of atherosclerosis [130]. CBD also protects the myocardium against ischemic reperfusion injury [131] and cannabidiol reduces

the cardiovascular damage caused by elevated blood glucose levels characteristic of DM, a major cause of death associated with DM [102,103]. In addition, increased *Cannabis* use following legalization of medical marijuana is correlated with a decrease in alcohol consumption [13], and alcohol use is associated with an increased risk of stroke [132]. The neuroprotective effects of *Cannabis* are likely to reduce the risk of death and the extent of damage from strokes. Thus, the relationship between *Cannabis* use and cardiovascular disease or mortality is complex. *Cannabis* probably causes some deaths and prevents others.

Jouanjus et al. [118] reported an average of 1.8 deaths/year from acute *Cannabis*-related cardiovascular accidents in France, a country with a regular user population of 1.2 million. Mittleman et al. [120] reported increased OR for CVA in the hour immediately following ingestion, and extrapolated an increased annual risk of a MI from 1.5 to 3% due to *Cannabis* use although they did not determine overall OR of users vs non-users. Rumalla et al. [112] detected an increased rate of acute ischemic stroke in *Cannabis* users, but the effect was modest (OR 1.17, 95% CI 1.15 – 1.20) a value lower than tobacco [112] and similar to the effect of ibupropen [133]. The magnitude of the response appears to be greatest in novice or occasional users and is rapidly attenuated with repeated use [110], so that longitudinal studies fail to detect increased rates of hospitalization in regular users [22-26]. Similarly, Barber et al. [115] and Westover et al. [134] reported overall OR for *Cannabis* use but both studies were rejected from the analysis, as follows. In the study by Barber et al. [115] only one patient did not also use tobacco, so no adjustment for tobacco use could be made, while Westover et al. [134] did not adjust for either alcohol or tobacco use. Evidence shows that *Cannabis* triggers acute CV accidents, this appears to be rare, similar to the risk posed by ibupropen and lower than tobacco, the risk appears to be rapidly attenuated in regular users, and regular use reduces multiple risk factors for cardiovascular disease.

<u>Meta-analysis</u>:

The available data shows no net effects of *Cannabis* use on mortality rates from cardiovascular disease, stroke, or MI, as multiple studies have failed to detect such effects [22-24,109-112,130,135]. *Cannabis* lowers risk of cardiovascular disease but also triggers acute cardiovascular accidents, effects that may counteract each other. A net effect of zero is used in the summary (Table 2). More research is needed in this area to identify delivery methods with lower risk, and people with cardiovascular disease who are considering initiation of medical use of *Cannabis* should be warned of the potential risk.

Effects on lung disease:

Numerous studies address effects of *Cannabis* use on lung and respiratory system health. While many articles report respiratory problems arising from *Cannabis* smoking, especially at high usage rates, it is clearly less harmful than tobacco [137]. No consistent association has been found between *Cannabis* use and lung cancer after accounting for confounding factors [138,139]. This result was supported by the current study, in which the mean adjusted odds ratio for lung cancer across those studies that met acceptance criteria was 1.03 (N = 4; supplemental excel file). On the other hand, reports of acute injury to lungs during *Cannabis* smoking are not uncommon, and heavy, chronic *Cannabis* use is clearly associated with increased airway resistance, symptoms of bronchitis, lung hyperinflation, and inflammation of the lungs as well as cellular changes resembling those caused by tobacco smoking prior to onset of cancer [140,141]. Case studies suggest that heavy *Cannabis* use may be associated with bulla formation or histopathological changes predisposing to emphysema, lung cancer, or pneumothorax [142-144] although a systematic review concluded that a causative link with bullae is unlikely [145] or represent uncommon responses in exceptionally heavy smokers [146]. A recent longitudinal study did not detect significant lung problems following 20 years of use [22]. There is also no clear link of *Cannabis* smoking with lung fibrosis as *Cannabis* use is associated with increased measures of lung volumes or capacities, including total lung capacity, forced vital capacity, functional residual capacity, or residual volume [22,34,139,140,146]. The data are inconclusive for increased rates of lower respiratory tract infections arising from the chronic bronchitis from frequent use [139]. Contaminants of *Cannabis* such as *Aspergillis* have been reported to cause serious lung problems in medical marijuana patients, especially those who are immunocompromised [147,148]. Patients should be made aware that the harms to the lungs and airways associated with smoking can be reduced by vaping [149], or eliminated with edible delivery methods.

Meta-analysis:

While frequent or heavy *Cannabis* smoking is associated with respiratory tract problems, and it may exacerbate the respiratory problems arising from tobacco use [150], *Cannabis* use by itself does not appear to increase mortality from respiratory problems, and no quantitative data on disease incidence or mortality are available for estimates of mortality from such problems. A net effect of zero is included in the meta-analysis of effects of *Cannabis* use on premature death

from lung disease (Table 2).

Effects on liver disease:

There are at this time no data showing changes in mortality from liver disease arising from *Cannabis* use. Cannabinoids both stimulate and inhibit liver fibrosis, depending on the receptor activated, and cannabinoids enhance liver steatosis [151-153] and may exacerbate effects of hepatitis C on the liver [154,155]. A cross-sectional study reported a strong correlation between daily marijuana use and moderate to severe liver fibrosis in individuals infected with HCV [155]. In another study, daily marijuana use was correlated with increased steatosis in patients with chronic hepatitis C [156]. However, a subsequent longitudinal study did not support causation of liver disease by *Cannabis* in such patients [157], finding no evidence that *Cannabis* use accelerated fibrosis (Hazard Ratio 1.02 (CI 0.93 – 1.12) or cirrhosis (HR 0.99 (0.88 – 1.12) [157]. Instead, the evidence was consistent with the correlation having arisen due to self-medication to treat the symptoms of liver disease [157]. Thus, *Cannabis* does not appear to increase mortality from liver disease in the absence of underlying disease states such as hepatitis C or toxin exposure, but may interact with other factors that cause harm to the liver.

On the other hand, legalization of medical marijuana results in a reduction in alcohol consumption [13], and reduces the use of prescription pain and other medications [12], actions that would reduce injury to the liver. For example, the popular over-the-counter pain medication acetaminophen was involved in 881 overdose deaths in 2010 [158] and is a common cause of liver toxicity. Combining acetaminophen and alcohol is especially harmful. Furthermore, nonalcoholic steatohepatitis is significantly correlated with obesity and insulin resistance, leads to cirrhosis, and is the third- most important indication for liver transplant [159,160]. The decrease in BMI and insulin resistance in *Cannabis* users [22,28-30,76,78,95,96] could therefore reduce nonalcoholic steatohepatitis in *Cannabis* users.

No published OR values for nonalcoholic steatohepatitis in *Cannabis* users, or data addressing whether mortality from liver disease is influenced by *Cannabis* use, were encountered during the search, but it is possible that *Cannabis* use could reduce deaths from liver disease due to these indirect effects. Patients should be urged to use strains high in CBD, or avoid high THC-low CBD strains, due to potential aggravation of harmful effects of other drugs and alcohol by activation of liver CB_1 receptors.

Meta-analysis:

Both beneficial and harmful effects of *Cannabis* use are detected, but no quantitative data showing relative rates of liver disease in users and non-users were identified that could be used in the analysis. The effect of *Cannabis* use on premature death from liver disease was detected in the study, and a value of zero is included in the meta-analysis (Table 2). Further research is strongly merited especially for potential beneficial effects and for further evaluation of the potential for harmful interactions with other drugs.

Effects on deaths from traumatic brain injury (TBI):

Cannabinoids have well known neuroprotective effects, reducing damage from excitotoxicity, Ca^{++} influx, free radical formation, and neuroinflammation following traumatic brain injury (TBI), ischemia, and neurotoxins [161-167,169-171]. Two studies were identified that addressed relative mortality rates of *Cannabis* users and non-users from traumatic brain injury [167,168]. Both these studies reported reduced mortality in *Cannabis* users, but only one [167] presented quantitative data on relative survival rates of *Cannabis* users and non-users. The study by O'Phelan et al. [168] reported an odds ratio of 0.33 for all illicit drug use but did not report data for *Cannabis* specifically, and was therefore excluded from the analysis. The remaining study [167] reported an odds ratio for mortality, following comparable TBI, of 0.224 ($P < 0.05$). This neuroprotective effect of *Cannabis* use in survival of brain injuries is supported by several clinical and laboratory studies. Knoller et al. [169] reported that patients with severe closed head injuries who were administered the synthetic cannabinoid HU-211 showed highly significant decreases in the duration of elevated intracranial pressures, reduced cerebral perfusion pressures, and decreased systolic blood pressures, and showed better outcomes at three and six months, relative to patients who did not receive the drug. Similarly, application of CBD to rats resulted in long-lasting neuroprotection from hypoxia and ischemia [170], and the endogenous cannabinoid 2-AG is neuroprotective following brain injury [171].

Of course, increased rates of TBI in *Cannabis* users would offset increased survival following injury. The evidence at this time does not support significant increases in rates of head injuries due to *Cannabis* use, however. Effects of *Cannabis* use on coordination are quite different from alcohol. Even at high doses, *Cannabis* has no noticeable effect on the ability of experienced users to ride a bicycle [172]. Several studies [22-27,173-174] were identified that addressed the

relative rates of injury, hospitalizations, or TBI in *Cannabis* users. Bechtold et al. [23] found no difference in incidences of concussions among *Cannabis* user groups. Kolakowsky-Hayner et al. [173] found no statistical differences in *Cannabis* use prior to brain and spinal cord injury, and Tait et al. [174] found that marijuana problems did not predict subsequent serious brain injury. Meier et al. [22] found no associations between persistent cannabis use and health outcomes in early midlife after years of use, and noted that the lack of effects was not driven by better health when *Cannabis* use was initiated [22]. Fuster et al. [25] identified no correlation between rates of emergency room admissions and frequency of *Cannabis* use. Gmel et al. [27] reported a dose-dependent reduction in risk of injury in *Cannabis* users (RR: 0.33; 95% CI = 0.12 - 0.92), though the sample size for *Cannabis* users was small. Two studies finding increased rates of hospitalizations were rejected. Ilie et al. [175] failed to account for alcohol use. Gerberich et al. [176] identified increased rates of injury hospitalizations in past and present *Cannabis* users, driven by increased motor vehicle accidents, assaults (men) and self- inflicted injuries. However, a recent major study found that the correlation of *Cannabis* use with motor vehicle accidents disappeared when the data were adjusted for confounding factors [177]. Assaults correlated with *Cannabis* appear to be linked to prohibition rather than *Cannabis* use itself as assaults and homicides have decreased in Colorado following legalization of *Cannabis* [178]. Self-injury would appear to be related to underlying mental health issues correlated with *Cannabis* use, and not *Cannabis* use itself [179]. Effects of *Cannabis* consumption on driving accidents are discussed below, and also do not support increased rates of head injury from automobile accidents due to *Cannabis* use.

Any increase in accident rates would need to be substantial to offset the reported increase in survival following injury (OR for death = 0.224) [167], and effects of this magnitude would be readily apparent. Available evidence thus suggests that the increased survival of *Cannabis* users following brain injury is not offset by increased injury rates arising from *Cannabis* use.

Meta-analysis:

Nguyen et al. [167] presented the only data that could be used to estimate effects on premature deaths. Justification of assumptions of causality arise from studies demonstrating neuroprotective effects of cannabinoids [161-166,169-171]. The CDC reports 53,014 traumatic brain injury deaths in 2013 [35]. Using these numbers, an estimated additional 3,003 to 5,019 deaths (estimated with a 12.2% user rate) would have occurred from TBI had no *Cannabis*

consumption taken place in 2013. These numbers are reported in the meta-analysis (Table 4). It is not clear what fraction of the reported percentage of the population using *Cannabis* each month would test positive at the time of injury, so this analysis may overestimate the impact of *Cannabis* use on deaths from TBI by assuming all *Cannabis* users who were in accidents tested positive at the time of the accident. However, cannabinoids linger in the body for a significant period of time following ingestion [180], and many of the patients who tested positive may not have been impaired at the time of the accident.

Effects on neurodegenerative and neuroinflammatory diseases and epilepsy:

Cannabinoids reduce the symptoms and progression of a number of neurodegenerative and neuroinflammatory diseases, including Alzheimer's disease, multiple sclerosis, amylotropic lateral sclerosis, Parkinson's disease, and Huntington's chorea [2,4-8,181-186]. They are also protective against toxins [164-166]. The data on Alzheimer's disease are particularly interesting. This disease is associated with neuroinflammation, excitotoxicity, oxidative stress, and reduced mitochondrial activity in the brain, and is characterized by the formation of aggregations of amyloid β peptide and neurofibrillary tangles [5]. Inflammation associated with microglia plays a key role in progression of Alzheimer's [184], and microglia-associated inflammation at senile plaques is strongly suppressed by low doses of THC [182]. Molecules of particular interest in Alzheimer's pathology, and thus in development of treatment options or preventative therapies, include acetylcholinesterase, glycogen synthase-3 (GSK-3β), phosphorylated tau, and amyloid β. Laboratory studies suggest that cannabinoids slow or stop the progression of Alzheimer's through actions on each of these targets. Low doses of THC inhibit the actions of acetylcholinesterase on amyloid β-peptide aggregation [181], and reduce levels of GSK-3β, phosphorylated GSK-3β, and phosphorylated tau protein, while simultaneously increasing mitochondrial activity [5]. Recently, Currais et al. [186] showed that THC caused dissociation of existing amyloid β plaques, characteristic of not only Alzheimer's disease but also associated with the general mental declines characteristic of the aging brain. These data are supported by Marchalant et al. [187], who showed that cannabinoids attenuate the neuroinflammation and decline in neurogenesis associated with aging in the mouse brain. Another recent study showed rejuvenation of the aging mouse brain through changes in gene expression, resulting in improvements in learning and memory, in response to low doses of THC [188]. Thus, laboratory studies show that THC and other

cannabinoid receptor agonists act via multiple pathways to reduce Alzheimer's pathology and improve function of the aging brain [2,5,6,128,181-188].

Other brain diseases also benefit from the neuroprotective and anti-inflammatory properties of cannabinoids. Parkinson's disease is caused by loss of dopaminergic neurons in the substantia nigra. *Cannabis* ameliorates the bradykinesia, rigidity, and tremor that are symptoms of Parkinson's disease, and reduces progression of the disease [4,7]. Multiple sclerosis, ALS, and Huntington's disease also benefit from cannabinoids [2,4,6,183]. *Cannabis* and cannabinoids reduce or, in a few patients, eliminate the frequent seizures of patients with treatment-resistant epilepsy [189]. Families of some such patients have become medical refugees, moving from states with more repressive policies to Colorado for legal access to potentially life-saving cannabinoids. Alzheimer's is reported as the cause of 84,747 deaths annually [35], although a recent study suggests that deaths from Alzheimer's may be as high as 503,000 annually [190]. Parkinson's disease is responsible for 25,196 deaths annually [35], while epilepsy causes approximately a three-fold increase in mortality [191] though specific numbers were not available from the CDC [35].

Meta-analysis:

There is clear theoretical evidence that *Cannabis* should reduce mortality from neurodegenerative and neuroinflammatory diseases, and may actually reduce the incidence or slow the onset of Alzheimer's and other diseases. However, no quantitative data showing relative rates of these diseases, or survival from these diseases, were identified in the analysis. Emerging evidence also shows significant neuroprotection against toxins and improved function of the aging brain. However, no data are available at this time showing relative incidences or mortality rates of Alzheimer's or other neurodegenerative diseases in *Cannabis* users and non-users. These diseases therefore could not be included in the estimates. However, a hypothetical 5% decrease in mortality from Alzheimer's disease due to *Cannabis* use, assuming that the age group prone to Alzheimer's disease uses *Cannabis* at a 3% user rate (lower than the national average among adults), results in prevention of an estimated 127 to 745 deaths each year. If this population used *Cannabis* at rates similar to the general population (12.2%), and upper estimates of deaths from Alzheimer's disease [190] are used in the analysis, *Cannabis* use would prevent or delay approximately 3,100 deaths annually due to Alzheimer's disease. In addition, Jones et al. [158] showed that antiepileptic and antiparkinsonism drugs contributed to 1,717 overdose deaths in

2010. Presumably, as with opioids, reducing use of these drugs through increased availability and use of *Cannabis* would reduce these overdose deaths as well. However, as we do not have odds ratios for incidence of or deaths from neurodegenerative diseases in *Cannabis* users, or for effects of medical marijuana on use of these drugs, a net effect of zero is included in the final estimates (Table 2). Further research is needed in this area.

Disorder	**Percent of population using *Cannabis***	
	12.2%	**Each 1% of adult population using Cannabis**
Cancer diagnoses	5,231 – 22,352	429 - 1,832
Cancer deaths	2,717 – 7,860	223 - 644
DM diagnoses	97,478	7,990
DM deaths	4,334 – 17,754	355 – 1,455
CV disease	No net impact detected	No net impact detected
Lung disease	No net impact detected	No net impact detected
Liver disease	No net impact detected	No net impact detected
Traumatic Brain Injury	5,019	411
Neurodegenerative diseases and epilepsy	Beneficial, quantitative data lacking	Beneficial, quantitative data lacking
Total deaths prevented	12,070 – 30, 633	989 – 2,511

Table 2: Summary of the separate meta-analyses showing estimated decreases in diagnoses and premature deaths of *Cannabis* use due to health impacts.

Estimates of effects of *Cannabis* use on diagnoses and premature deaths, at the reported population user rates of 12.2%, and for each 1% change in the proportion of the population using *Cannabis*, are reported for physical health parameters hypothesized to be influenced by *Cannabis* use. Odds ratios were only available for cancer, DM, and TBI, and these all showed a decrease in death rates with *Cannabis* use. Available data do not support net increases in mortality from cardiovascular disease, liver disease, or lung disease due to *Cannabis* use, while evidence supports prevention of deaths from neurodegenerative diseases and epilepsy but quantitative data are lacking.

Changes in the mortality rate following legalization of medical marijuana.

In order to more completely estimate the impact of *Cannabis* use on premature deaths, the effects of legalization of medical marijuana were also investigated. Driving fatalities, opioid overdose deaths, and alcohol consumption have all been found to decrease following legalization of medical marijuana. The apparent impact of medical marijuana on the mortality rate from these causes is estimated below.

Calculations to estimate the impact of legalization of medical marijuana on the mortality rate:

Legalization of MMJ has been reported to influence suicides, opioid overdose deaths, driving fatalities, and alcohol use. The impact of *Cannabis* use on each of these causes of death was explored further using Google scholar and PubMed as described above. The number of fatalities from these causes prevented or caused by medical *Cannabis* use (MMJ) in the United States each year, and the total since 1996, was estimated using formula 2, with E and D as in formula 1.

Formula 2: E = D(%change/100)

The change in numbers of deaths from each cause, per state, is estimated by assuming a random distribution of deaths across all states based on their population. Data on the total numbers of fatalities/year from each cause [35] are multiplied by the fraction of the U.S. population living in each state with legal access to MMJ (as of 2015; obtained from the U.S. census) to arrive at a rough estimate of the number of fatalities occurring per year from that cause in that state (Table 3). Formula 2 is then used with these data to estimate the impact of *Cannabis* use on fatalities from each cause of death per year in each state. This is by necessity an initial rough estimate ignoring heterogeneity among states. The results were then summed across states to determine the impact of legalization of medical marijuana nationwide. To estimate the deaths prevented if MMJ was legal nationwide, formula 2 was applied to the total annual number of deaths from each cause nationwide.

Effects of medical marijuana on fatal opioid overdoses:

Opiate prescription painkillers are widely used, high risk drugs with strong potential for abuse, addiction and fatal overdose. Opioid overdose deaths are spiking, and medical *Cannabis* use has been shown to reduce opioid dose and usage by as much as 64% in the treatment of chronic pain, reducing side effects and improving quality of life [194-197]. Data such as these lead to the proposition that medical *Cannabis* use is a safer option to reduce the harm and morbidity from opioid use for treatment of pain [196]. This proposal is supported by the demonstration that legalization of medical marijuana leads to significant drops in hospitalizations from opioid pain reliever, without impacting hospitalizations related to marijuana [197]. States legalizing MMJ have seen a reduction of 24.8% in the rate of fatal opioid

overdose deaths in the first 5 years following legalization, and a 33% decrease after 5 years, relative to states without such legal access [192]. About 60% of the fatalities had resulted from a prescription obtained from a single provider, suggesting that many of these deaths were accidental overdoses during treatment of pain [192]. This decrease in OD deaths held up when suicides were eliminated from the data set, and appears to arise from substitution of *Cannabis* for opioids [10-12,194-199]. It should be noted that many overdose deaths involve prescription drugs other than opioids [158]. For example, in 2010 there were 3,889 reported overdose deaths from antidepressants, 2,239 in combination with opioids, 1,717 from antiepileptic and antiparkinsonism drugs, 1,125 in combination with opioids, 6,497 overdose deaths from benzodiazepines (used to treat anxiety, insomnia, and as a muscle relaxant), 5,017 in combination with opioids), 881 overdose deaths from acetaminophen, and 228 from NSAIDS [158]. Most medical marijuana patients (80%+) report substituting *Cannabis* for prescription drugs, citing less adverse side effects and better symptom management [10-12,196-199].

State	Fraction of US population
AK	0.2%
AZ	2.1%
CA	12.2%
CO	1.7%
CT	1.1%
DE	0.3%
HI	0.4%
IL	4.0%
ME	0.4%
MD	1.9%
MA	2.1%
MI	3.1%
MN	1.7%
MT	0.3%
NV	0.9%
NH	0.4%
NJ	2.8%
NM	0.7%
NY	6.2%
OR	1.2%
RI	0.3%
VT	0.2%

WA	2.2%
DC	0.2%

Table 3: State legalization and census data used to estimate effects of medical marijuana on death rates. States legalizing medical marijuana as of 2015 are included in the analysis. For each state that has legalized medical marijuana, the state population as a percentage of the total US population is shown. Data on total U.S. and state populations were obtained from the U.S. census. These data are used to estimate changes in death rates from reported changes in opiate OD, driving fatalities, and alcohol for each state following legalization of MMJ.

Cause of death	Fatalities/ year	Annual deaths prevented in states with legal MMJ	Annual deaths prevented if MMJ was legal nationwide
Opiate OD	16,235	2,227	4,759
Alcohol, excl. driving	77,924	1,823 to 3,865	3,859 to 8,258
Driving fatalities	35,369	1,324 to 1,820	2,829 to 3,890
Total	**129,528**	**5,400 to 7,900**	**11,500 to 16,900**

Table 4: Summary of meta-analysis of estimated reductions in premature deaths following legalization of medical *Cannabis*.

Opioid overdose fatalities: Estimates are based on 16,235 prescription opioid overdose fatalities nationwide/year for 2013 [35]. For years 1-5 following legalization, a reduction of 24.8 % was used in calculations, whereas for years 6- present post-legalization the reduction of 33% was used, as reported by Bachhuber et al. [192].

Driving fatalities: Estimates of changes in driving fatalities are based on 35,369 driving fatalities/year nationwide [35]. Data on the reduction in driving fatalities was estimated using the 8 to 11% decrease following legalization, as reported by Anderson et al. [13].

Other alcohol-related deaths: Alcohol-related deaths from causes other than driving fatalities were estimated using 88,000 alcohol related deaths/year (National Institute on Alcohol Abuse and Alcoholism [193]), from which the estimated numbers of drunk driving fatalities/year were subtracted, giving an 77,924 alcohol-related non-driving deaths nationwide. A lower estimate for the decrease in alcohol related deaths other than driving was established using the 5% decrease in overall alcohol consumption, and an upper estimate using the 10.6% decrease in numbers of drinks consumed, as reported by Anderson et al. [13]. These data were used in conjunction with data on the proportion of the U.S. population living in states with legal MMJ.

Meta-analysis:

Assumptions of causality are clearly justified by the substitution of *Cannabis* for pharmaceutical pain relievers [10-12,194-199]. Bachhuber et al. [192] presented the only data

that could be used to estimate impacts on mortality rates. Using the 24.8% reduction in the first 5 years and 33% reduction thereafter, this rate of reduction in overdose deaths translates to an estimated 2,227 fewer overdose deaths/year in 2015 in states with legal medical marijuana. If MMJ were legal nationwide, this number would increase to 4,800. This number does not account for people who illicitly reduced opioid use with *Cannabis* prior to legalization or do so at present in non-MMJ states.

Recently, Bradford and Bradford [13] showed that legalization of medical marijuana was associated with decreases in prescriptions for drugs to treat pain, nausea, psychosis, seizures, sleep disorders, depression, and spasticity, suggesting that overdose deaths from non-opioids used to treat these conditions should decrease as well. In addition, medical *Cannabis* use is associated with reduced use of alcohol [10,11,13] and mixing alcohol with prescription drugs greatly increases the risk of harm. Thus, it is likely that substitution of *Cannabis* for these other pharmaceuticals, and for alcohol, would further reduce overdose deaths. An analysis to test this hypothesis has not been performed to date and no data are available for inclusion in the meta-analysis.

Effects of medical marijuana on alcohol consumption:

Alcohol is a high risk drug [200,201]. The National Institute on Alcohol Abuse and Alcoholism reports approximately 88,000 alcohol-related deaths/year in the US [193]. The relative risks posed by drugs can be quantified using the margin of exposure (MOE), defined as the ratio between the toxicological threshold and the estimated human intake. Low MOE numbers indicate high risk. For individual users, the MOE for alcohol is less than 10, signifying high risk, whereas the MOE of THC is > 100, the lowest risk category. For the overall population, alcohol also ranks as a much higher risk, with MOE < 10 compared to *Cannabis* with MOE > 10,000 [200,201]. Thus, according to any objective analysis alcohol is far more dangerous than *Cannabis*. Alcohol causes mortality in several ways, including acute overdose, increased risk of driving fatalities and other fatal accidents, and chronic liver disease, and alcohol use is strongly correlated with violent crimes including assault, domestic violence, and homicide [202]. Alcohol ranked as the fifth leading risk factor for disease in 2010, with an average of 25,793 deaths/year in the US from direct health effects of alcohol [202]. Replacement of alcohol with *Cannabis* should therefore reduce the death rate.

The relationship between *Cannabis* use and alcohol consumption is complex [203]. *Cannabis* has been found to substitute for alcohol in MMJ patients [10,11,13,198-199], and alcohol and tobacco use by teens increases during periods of *Cannabis* abstinence and decreases again upon resumption of *Cannabis* use, though these effects were not observed in individuals who remained abstinent after one month [204]. In contrast, decriminalization appears to have little consistent impact on alcohol use [reviewed by 203], while *Cannabis* use predicted increased incidence of alcohol use disorder in a longitudinal study [205].

Effects of MMJ legalization on driving fatalities and other alcohol-related deaths are analyzed separately below, because we have data specifically addressing effects of legalization of medical, but not recreational, marijuana on driving fatalities.

Effects of medical marijuana on driving fatalities:

Effects of Cannabis intoxication on driving: The effects of *Cannabis* on driving are clearly distinct from, and less detrimental than, alcohol [206]. Effects of *Cannabis* use on mortality rates are not clear-cut. Recent reviews found that studies on effects of acute *Cannabis* intoxication on driving fatalities have inconsistent results, with some studies reporting increased risk, some no effect, and some decreased risk in users [207-209]. Following meta-analysis, Asbridge et al. [207] concluded that acute *Cannabis* intoxication approximately doubled the risk of fatal collisions (OR for collisions = 1.92, OR for fatal collisions = 2.1, OR for culpability = 1.65). Another systematic review and meta-analysis failed to detect any significant effect of *Cannabis* use on fatal (OR 1.26, 0.88 – 1.81) or injury (OR 1.10, 0.88 – 1.39) crashes when data were adjusted for publication bias and other confounding factors [208]. A significant increase in property damage remained following adjustment, however (OR 1.26, 1.10 – 1.44) [203]. Li et al. [209] obtained a summary odds ratio of 2.66 for crash risk.

Following these studies, the "Crash Risk" study was performed by the National Highway Traffic Safety Association (NHTSA). In this, the largest study on crash risk associated with drug use in the U.S. [177], 3,000 crash-involved drivers and 6,000 control drivers were analyzed for illicit drug and alcohol use. The unadjusted OR for *Cannabis* use and crash risk was 1.25 (P = 0.01), resembling the results of Elvik [208]. However, adjustment of the data for age, gender, and race/ethnicity further reduced the OR to 1.05 (P = 0.65), and additional adjustment for alcohol use reduced it further still, to a final OR of 1.00 (P = 0.98). In other words, this study, the largest

of its kind, detected absolutely no impact of *Cannabis* use on crash risk [177] despite being sufficiently sensitive to show dose-dependent increases in blood alcohol levels well below the legal limit. Drivers at the legal alcohol limit showed a four-fold increase in crash risk. Similarly, a longitudinal study of a birth cohort did not show increased risk of driving fatalities among *Cannabis* users when the data were adjusted for risky behaviors correlated with *Cannabis* use [210]. Thus, the evidence that *Cannabis* use increases the mortality rate from driving fatalities is weak, and the correlation may be driven by other factors, such as sex, age, and other confounding factors. This is supported by a series of studies that fail to find increased utilization of emergency services or hospitalizations by long-term *Cannabis* users [22-27, 173-174]. Furthermore, increased risk during acute *Cannabis* intoxication does not necessarily translate into increased crashes or mortality at the population level, because users may alter behavior when using *Cannabis.* Possible compensatory changes include driving less often or shorter distances, avoiding roadways with higher speed limits, reducing alcohol consumption, or otherwise altering the overall risk of crashes.

Effect of changes in the legal status of *Cannabis* on driving fatalities:

Legalization of marijuana provides a natural experiment to determine population-level changes in marijuana use on driving fatalities. Driving fatalities have been declining overall, for decades [211], Legalization of both medical and recreational marijuana use have been correlated with decreases in driving fatalities [13,211,212]. Anderson et al. [13] showed that driving fatalities decrease by 8 to 11% in the year following legalization of medical marijuana, a decrease driven primarily by reduced alcohol-related driving deaths. Santaella-Tenorio analyzed data from states legalizing medical marijuana, and showed a immediate post-legalization decrease in traffic fatalities of 10.8% [211]. Santaella-Tenorio et al. [211] performed an extensive analysis of driving fatalities in states legalizing medical marijuana, using data from the 1985 – 2014 Fatality Analysis Reporting System. This study supported the analysis of Anderson et al. [13], showing immediate reductions in traffic fatalities among drivers aged 15-24 yo, and additional yearly decreases among those aged 25-44, though no effects on older age groups were observed. Dispensaries were also associated with decreases in fatalities among those aged 25-44 [211]. As drivers aged 24-45 are disproportionately represented in driving fatalities (47%), this suggests that medical marijuana legalization has the greatest impact on the population at greatest risk for driving fatalities [211]. There was heterogeneity among states, with a couple of states showing

increased fatalities while most showed decreases. The overall effect was a reduction of 10.8% in traffic fatalities in states legalizing medical marijuana, with California and New Mexico showing the largest immediate post-MMJ decreases, of 16% and 17.5% respectively, whereas Michigan saw an increase. As California is the largest state with legal access, the immediate, large decrease in fatalities would make an especially pronounced contribution to the effect of legalization on driving fatalities. Balko [212] analyzed data from the Colorado Department of Transportation, and showed that driving fatalities decreased following legalization of recreational use. Illicit *Cannabis* use may therefore decrease driving fatalities in other states where it remains illegal, an effect that was invisible until revealed by changes in legal status, though replicated data from states legalizing recreational *Cannabis* use are not yet available.

The data presented by Anderson et al. [13] are used in the analysis because they are the only numerical values encountered during the search that can be entered into Formula 2 (Balko [212] did not give numerical data). Odds ratios for driving fatalities when acutely intoxicated cannot be used to estimate effects of *Cannabis* use on driving fatalities from the values for the proportion of the population using *Cannabis* each month, as it is not clear how many users consistently drive when acutely intoxicated.

The proportion of drivers involved in fatal accidents who test positive for *Cannabis* use has increased in Colorado [213] and Washington State [214] following legalization. However, like overall risk during acute intoxication, this does not mean that *Cannabis* use increases population level crash risk, as these studies did not include controls who were not involved in accidents. If the proportion of drivers testing positive for *Cannabis* use who were not involved in a crash increased by the same amount as those who were, then *Cannabis* does not alter crash risk. As these data were not presented it is not possible to claim that observed increases in *Cannabis* use have caused an increase in crashes following legalization. In fact, data from the Colorado Department of Transportation show that driving fatalities decreased in Colorado following legalization of recreational use [212] despite evidence for large increases in the numbers of drivers testing positive for *Cannabis* [214]. Thus, it appears that, while driving under the acute influence of *Cannabis* may increase the risk of crash, driving fatalities paradoxically decrease following legalization of medical and recreational *Cannabis* use, possibly due to changes in driving behavior or substitution of *Cannabis* for alcohol, which clearly has far greater impact on driving safety [10-11,13,206,211-212].

Meta-analysis:

Assumptions of causation are justified by the relative impacts of *Cannabis* and alcohol use on driving [206] and on coordination [172], and the decrease in alcohol use upon legalization or initiation of medical marijuana [10-11,13]. For the current analysis, the most relevant studies for estimates of effects on mortality rates are those documenting changes in fatalities following changes in the legal status of *Cannabis*. Anderson et al. [13] reported an immediate post-MMJ decrease in traffic fatalities of 8-11%, while Santaella-Tenorio et al. [211] reported a very similar immediate decrease of 10.8%.

According to the CDC [210], there were 35,369 driving fatalities in the U.S. in 2013. Using the data presented by Anderson et al. [13], an estimated 1,300 to 1,800 fewer driving fatalities/year in states with legal medical marijuana, and 12,800 to 17,500 fewer driving fatalities total since legal access began (Table 4). Had medical marijuana been legalized nationwide in 1996, an estimated 53,750 to 73,900 fewer driving fatalities would have occurred during this time. These numbers are likely underestimates of the impact of *Cannabis* use, as the rate of drunk driving fatalities has decreased during this period and illicit *Cannabis* users may well have already shown reduced risk prior to legalization.

Effects of medical marijuana on other alcohol-related fatalities:

Evidence for changes in alcohol use due to decriminalization or legalization of recreational marijuana are mixed [203]. A recent review supports both substitution and complementarity of *Cannabis* and alcohol under different conditions, finding that more liberal *Cannabis* laws are associated with reduced alcohol consumption [215]. The overall impact of recreational *Cannabis* use on alcohol use is therefore unclear. There is strong evidence, however, that legalization or use of medical marijuana reduces use of alcohol and prescription drugs [10-13,194-199]. If medical marijuana reduces alcohol use, it is expected to reduce non-driving alcohol-related fatalities.

Meta-analysis:

While the relationship between recreational Cannabis use and alcohol use is not yet clear, available data suggest that medical marijuana is associated with a decrease in alcohol consumption [10,11,13,198-199]. To obtain an estimate of non-driving alcohol-related fatalities,

reported numbers of drunk driving fatalities (10,076/year; [216]) were subtracted from total estimates of alcohol-related deaths (88,000/year; [193,202]) to give 77,924 alcohol related fatalities/year from remaining causes. Assuming a linear relationship between consumption and risk, the reported 5% decrease in alcohol consumption in states following legalization of MMJ [13] gives an estimated decrease in non-driving alcohol-related deaths of 1,800 deaths/year (Table 4). Had the observed 10.6% reduction in number of drinks consumed during a drinking episode [13] been used in the analysis instead, this estimate would increase to 3,900 non-driving alcohol-related deaths prevented each year. These numbers are used as lower and upper estimates of the impact of medical *Cannabis* use on the alcohol-related mortality rate (Table 4). If MMJ were legal nationwide, these numbers would increase to 3,900 to 8,300 deaths prevented each year.

Effects of medical marijuana on suicide:

Anderson et al. [217] analyzed state level suicide data from the National Vital Statistics Systems Mortality Detail files from 1990 to 2007, and found that suicide rates decreased 9.2 to 10.8% in young men aged 20-29, and 9.4 to 13.7% in men aged 30-39, in states legalizing MMJ relative to states with no legal access. No change was observed in suicide rates among young women [217]. However, subsequent studies that adjusted for additional confounding factors failed to detect a change in suicide rates following legalization of MMJ [218,219]. The estimate used in the current analysis is therefore a net change of zero in annual suicides in response to legalization of medical marijuana. Note that none of the studies found an increase in suicide rates.

Summary of effects of *Cannabis* on the mortality rate:

Published data show clear evidence for reduced deaths from cancer, diabetes mellitus, traumatic brain injury, in *Cannabis* users, and reduced deaths from opioid overdose, alcohol consumption, and driving fatalities. The greatest impacts of *Cannabis* use on the death rate are from effects of *Cannabis* use on rates of diabetes mellitus and cancer. These decreases are primarily associated with "recreational" use rather than medical use. The number of deaths from cancer, DM, and TBI decreases by an estimated 989 to 2,511 deaths for each 1% of the population using *Cannabis*. In addition, legalization of MMJ prevents an estimated 5,400 to 7,900 deaths each year in states with legal access, from reduced opioid overdose deaths, driving fatalities, and alcohol use. Under the regulatory policies in place in 2015, the effects of *Cannabis* use on

mortality rates from all causes of death is estimated to be the prevention of between 17,400 to 38,500 deaths prevented/year assuming that 12.2% of the population uses *Cannabis*. If MMJ was currently legal in all states, the total reduction in premature deaths would increase to 23,500 to 47,500 at a 12.2% user rate (Table 5, Figure 4).

These numbers are likely underestimates for several reasons. Laboratory studies suggest that *Cannabis* use reduces the incidence or progression of neurodegenerative and neuroinflammatory diseases, epilepsy, and harm from exposure to neurotoxins [4-7,161-167,181-186]. Alzheimer's disease is responsible for a reported 84,747 [35], and possibly the underlying cause of as many as 503,000 premature deaths annually [190], while Parkinson's disease is responsible for 25,196 deaths/year [35]. However, odds ratios for the effects of *Cannabis* use on incidences of or mortality from these neurodegenerative diseases are not available. Cannabinoids have also proven effective in reducing or eliminating the seizures characteristic of treatment-resistant epilepsy [189]. Furthermore, anti-epileptic and anti-Parkinsonism drugs caused 1,717 fatal overdoses in 2010 [158]. DM deaths are also likely underreported causing underestimation of DM deaths prevented by *Cannabis* use [107,108].

Medical marijuana patients substitute *Cannabis* for prescription and illicit drugs [10-12,194-199]. Drugs involved in overdose deaths include opioids, benzodiazepines, antidepressants, antiepileptic and antiparkinsonism drugs, antipsychotic and neuroleptic drugs, acetaminophen, barbiturates, NSAIDS, and muscle relaxants [158]. Recently, Bradford and Bradford [12] showed that prescriptions for drugs used to treat pain, anxiety, nausea, psychosis, seizures, sleep disorders, depression, and spasticity decrease following legalization of medical marijuana [12], yet data are not available for effects of legalization of MMJ on overdose deaths from drugs used to treat these conditions, other than opioids. Illicit use of *Cannabis* most likely reduced mortality rates from driving fatalities and overdoses prior to legalization, as the effects of *Cannabis* use on these causes of death only became visible when legal access increased the pool of people using *Cannabis*. Finally, homicides and assaults are down in Colorado following legalization of recreational marijuana [178], although this most likely arises from cessation of prohibition rather than from *Cannabis* use itself. The present work therefore almost certainly significantly underestimates the number of premature deaths prevented by *Cannabis* use in the U.S. If so, further decreases in the mortality rate are expected with improved legal access.

Scenario	Deaths prevented	Deaths prevented
	Lower estimate	Upper estimate
12.2% user rate, under current medical	**17,400**	**38,500**
12.2% user rate, with legal medical MJ	**23,500**	**47,500**

Table 5: Summary of the meta-analysis: Estimated lives saved per year by *Cannabis* use, from all causes.

'Current medical policies' includes states with legal access to medical marijuana in 2015, while 'legal medical MJ nationwide' gives estimates assuming legal MMJ in all states.

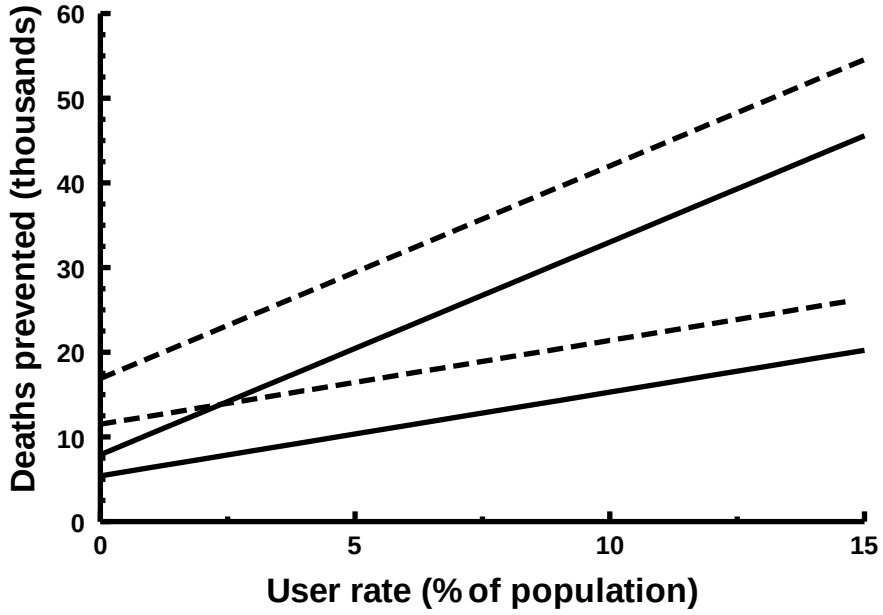

Figure 4: Estimated annual numbers of premature deaths prevented by *Cannabis* use in the United States. The solid lines show estimated premature deaths prevented by *Cannabis* use under current medical marijuana policies (as of 2015). At the Y intercept are the deaths prevented by medical marijuana, while the slope represents the additional deaths prevented by "recreational" use as a function of the percent of the population using *Cannabis*. The dashed lines show the number of premature deaths that would be prevented by *Cannabis* use if medical marijuana were legal nationwide, with the Y intercept the deaths prevented by medical marijuana alone and the slope showing the additional effects of recreational use, as above.

<u>Summary of the risk of bias across studies</u>:

Prior reviews, by including only adverse effects of *Cannabis* use and ignoring beneficial

effects, have grossly misrepresented the public health impact of *Cannabis* use in the U.S. This has fed misconceptions of the public health impact of *Cannabis* use that have influenced research priorities and government policies.

Estimation of the numbers of deaths caused by *Cannabis* prohibition:

If *Cannabis* reduces the mortality rate, a hypothesis strongly supported by the analysis above, and assuming that prohibition decreases the number of people using *Cannabis*, then prohibition must increase the mortality rate. Evidence that prohibition decreases the number of people using *Cannabis* is clearly seen in changes following legalization of medical marijuana, and in Colorado following legalization of recreational marijuana. The current analysis shows that the difference in deaths from opioid overdose, driving fatalities, and alcohol-related causes in states that have legalized medical marijuana (MMJ) and those that have not is an estimated 6,100 to 9,000 deaths/year. These deaths can be directly attributed to prohibition. Note that these deaths can be attributed to prohibition even if prohibition has no effect on the "recreational" user rate. We can add to this number the increased deaths from cancer, diabetes mellitus, and traumatic brain injury that occurred because prohibition caused people to abstain who would otherwise use *Cannabis*. Each 1% decrease in the proportion of the population using *Cannabis* results in an estimated 989 to 2,511 additional premature deaths each year. The amount by which the user rate is decreased by prohibition is not known. If, however, prohibition causes a 3% decrease in *Cannabis* use (from 15.2 to 12.2%), and deaths from lack of access to MMJ are included, prohibition is responsible for an estimated 9,100 to 16,500 deaths each year, in the range of the mortality rate from opioid overdose (16,235) or homicides (16,121). A 7% decrease in the user rate would cause more deaths than Parkinson's disease (25,196) [31](Figure 5). These calculations are almost certainly underestimates of the effects of prohibition, for reasons described above. Furthermore, prohibition has also almost certainly prevented the development of life-saving medicines and significant refinements in the medical use of *Cannabis* leading to additional deaths.

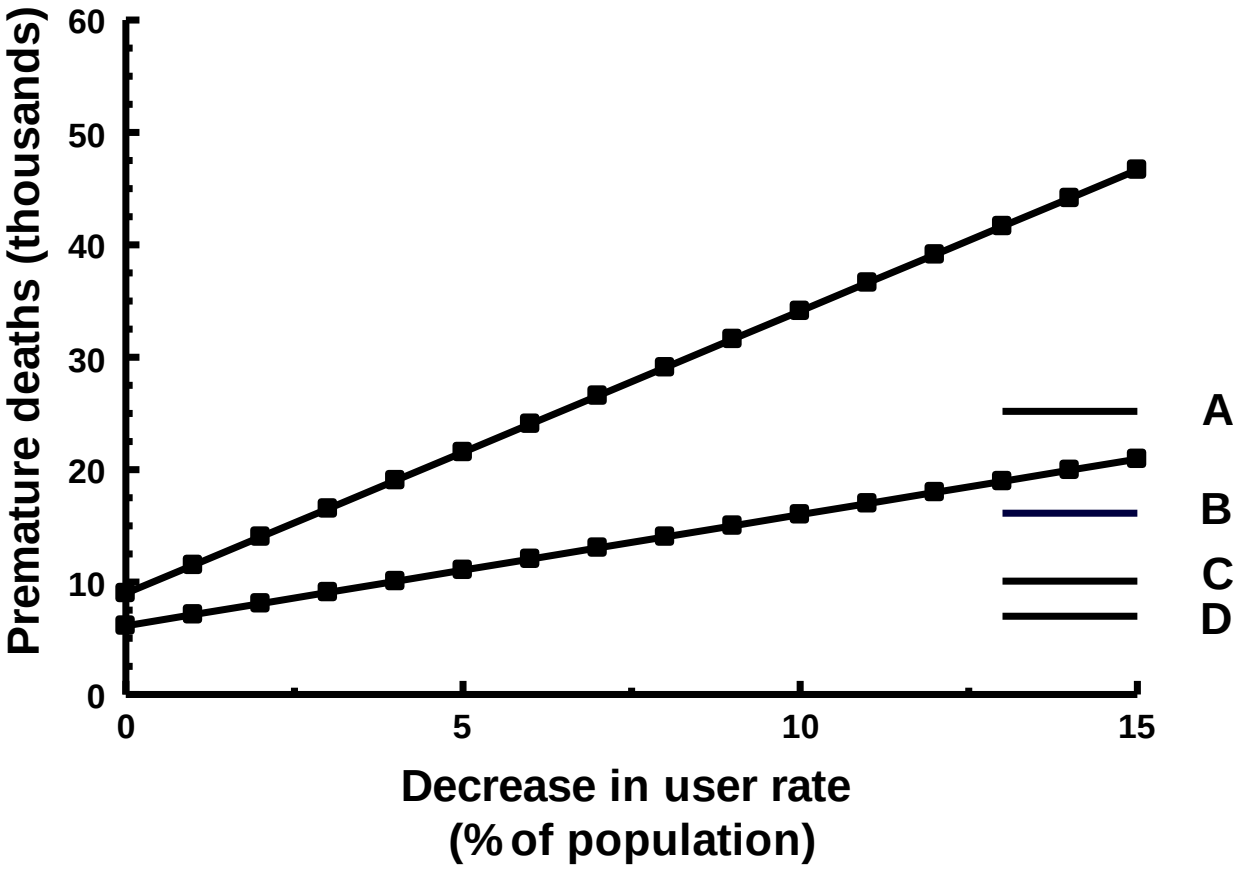

Figure 5: Annual estimates of premature deaths due to prohibition. The decrease in the percent of the population using *Cannabis* represents the effectiveness of prohibitionist policies. The Y-intercept shows the lower and upper estimates of the deaths attributed to lack of access to medical marijuana under current policies (as of 2015). The slopes of the lines are the 989to 2,511 additional deaths that occur each year from cancer, DM, and TBI for each 1% decrease in the user rate. The X- axis is the decrease in the proportion of the population using *Cannabis* in response to prohibition. The dashed lines show the numbers of deaths in 2010 from (A): Parkinson's disease, (B): homicides or opioid overdose, (C): drunk driving, and (D): HIV.

Conclusions:

This initial attempt to estimate the overall public health impact of *Cannabis* use, including both beneficial and harmful impacts on health, using published data, clearly suggests that *Cannabis* use is associated with a substantial decrease in the premature death rate.

Based on the results of this extensive review of the evidence, it is time to change the discussion, from determining how much harm is caused by *Cannabis* use, to determining how many deaths are prevented by *Cannabis* use. This does not, of course, mean that *Cannabis* has no

harmful effects, just that beneficial effects may outweigh harmful effects on physical health. The most important determinant of health status is continued survival, and the results of this investigation strongly support the hypothesis that *Cannabis* use is associated with improved survival.

The results of this analysis differ significantly from other recent studies that attempt to determine the public health impact of *Cannabis* use [18-21]. The current work includes factors (DM, cancer, TBI, MMJ) for which *Cannabis* use is associated with decreased mortality, effects that were either not known at the time, [19] or were not included [20,21] in prior analyses. The current analysis is also at odds with a number of studies that fail to detect changes in health or emergency room visits with *Cannabis* use [22-27]. The most likely cause of this discrepancy is that these longitudinal studies did not follow subjects long enough, as the longitudinal studies to date follow younger cohorts for 15 – 20 years, into their mid-thirties or early middle age [22-23]. Decreased mortality from obesity-related diseases and cancer in *Cannabis* users would most likely not become apparent until later in life. For example, the decrease in rates of diabetes mellitus observed by Rajavashiseth et al. [76] was only apparent in subjects aged 40 – 59, and death from obesity-related conditions such as diabetes mellitus may take many years after onset of the disease.

The results of the current analysis strongly suggest that *Cannabis* prohibition is a significant failure of public health policy, causing more harm than benefit. In addition to increasing the mortality rate, prohibition contributes to the largest per capita prison population in the world, interferes with pursuit of promising medical research, results in the loss of billions in potential tax revenues, empowers violent drug cartels thus destabilizing governments of neighboring countries, and causes extensive economic and electoral disenfranchisement of the most vulnerable U.S. communities. Furthermore, evidence available at this time suggests that prevention of *Cannabis* use by football players, people who are pre-diabetic or diabetic, people who may develop or have cancer, people suffering from chronic pain, epilepsy, Parkinson's disease, multiple sclerosis, Alzheimer's disease, and people who have been exposed to violence decreases their quality of life and/or increases their risk of death. This would seem to be a violation of basic human rights, especially as *Cannabis* is objectively less toxic than the widely used over-the-counter analgesic acetaminophen and many prescription drugs [158]. At present, prohibition creates the appearance that the criminal justice system is using taxpayer money to

protect the profits of the pharmaceutical and private prison industries, in the process contributing to the systemic racism and voter disenfranchisement plaguing this country [223,224]. It is time to demand that politicians and the criminal justice system justify, if they can, the continuing harm caused to society by *Cannabis* prohibition when recent polls show that the majority of Americans support legalization.

Limitations of this study:

This study focuses on effects on premature death rates and does not claim that *Cannabis* has no harmful effects on individual health or society. Causes of morbidity that do not directly increase the death rate, such as *Cannabis* use disorder, are outside the scope of the study. The study focuses on population-level effects, which are by effects on the average user, rather than the worst outcomes arising in individuals with the highest levels of use. Estimates of impact of legalization of medical marijuana are based on average decreases across states and do not consider differences in population or demographics of individual states. The estimates are based on existing data revealed during extensive database searches, and these searches may have missed important data. Estimates of effects of *Cannabis* on the mortality rate from causes including neurodegenerative diseases and neurotoxins, epilepsy, those cancer types responsible for 30% of cancer diagnoses and 39% of cancer deaths, overdose deaths from prescription drugs other than opioids, and violence associated with *Cannabis* prohibition were not encountered during the search and were not included. The study is thus likely to underestimate significantly the actual impact of *Cannabis* use on the premature death rate. The numbers provided are thus rough estimates based on existing data, and it is anticipated that more refined analyses of more complete data will provide more accurate values. This study does not consider the indirect health effects of decreased life-long income due to the impact of drug law violations or *Cannabis* use on educational or employment opportunities.

Declarations:

- Ethics approval and consent to participate: The analysis used published data, so ethics approval and consent to participate are not applicable.
- Consent for publication: not applicable.
- Availability of data and material. A summary of the cancer data used in the analysis are available in the supplemental excel file. The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.
- Competing interests: The author claims no competing interests.

- Funding: The author did not receive funding for this analysis.
- Author contributions: there is only one author who is responsible for all content.

Acknowledgements: I would like to thank my students and colleagues at IUSB for inspiring and supporting this research, and Kirk Mecklenburg and Murlidharan Nair for helpful comments on an earlier version of this work.

Authors' information: Thomas Clark is Professor and Chair of Biological Sciences at Indiana University South Bend, where he teaches Human Anatomy and Physiology, Organismal Physiology, and Entomology, and has taught a Master's course on the therapeutic and legal aspects of marijuana for the MLS program. He obtained his PhD in Comparative Physiology from the Department of Ecology and Evolutionary Biology at the University of California Irvine, in 1994.

Abbreviations:

MMJ; medical marijuana.
TBI; traumatic brain injury
OR; odds ratio
RR: relative risk
HR: hazard ratio
DM; diabetes mellitus
THC: Δ^9-tetrahydrocannabinol
CBD: Cannabidiol
CB1 and CB2: classes of cannabinoid receptors
HNSCC: head and neck squamous cell carcinoma
US; United States
LDL; low density lipoproteins
HDL; high density lipoproteins
COPD: chronic obstructive pulmonary disease
FEV1: Forced expiratory volume, 1 second.

References:

1. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: from the early to the latest concepts. Best Pract Res Clin En. 2009;23:1-15.
2. Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 2000,404: 84-7.
3. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. J Ethnopharm. 2006;105:1-25.
4. Bisogno T, Di Marzo V. Cannabinoid receptors and endocannabinoids: role in neuroinflammatory and neurodegenerative disorders. CNS Neurol Disord - DR 2010;9:564-73.
5. Cao C, Li Y, Liu H, Mayl J, Lin X, Sutherland K, Nabar N, Cai J. The potential therapeutic effects of THC on Alzheimer's disease. J Alzheimers Dis. 2014;42:973-984.
6. Jackson SJ, Diemel LT, Pryce G, Baker D. Cannabinoids and neuroprotection in CNS inflammatory disease. J. Neurol Sci. 2005;233:21-5.
7. Lotan I, Treves TA, Roditi Y, Djaldetti R. Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study. Clin Neuropharmacol. 2014,37:31-44.
8. Naftali T, Schleider LB-L, Dotan I, Lansky EP, Benjaminov FS, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013;11:1276-80.
9. Osborn LA, Lauritsen KJ, Cross N, Davis AK, Rosenberg H, Bonadio F, Lang B. Self-medication of somatic and psychiatric conditions using botanical marijuana. J Psychoactive Drugs. 2015;47(5):345-50.
10. Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay R, Capler R, Holtzman S. Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: the impact of contextual factors. Drug Alc Rev. 2015; DOI:10.1111/dar.12323.
11. Lucas P, Reiman A, Earleywine M, McGowan SK, Oleson M, Coward MP, Thomas B. Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution effect in Canadian medical cannabis patients. Addict Res Theory. 2013;21:435-42.
12. Bradford AC, Bradford WD. Medical marijuana laws reduce prescription medication use in Medicare part D. Health Aff 2016;35:1230-6. doi:10.1377/hlthaff.2015. 1661. pmid:27385238
13. Anderson DM, Hansen B, and Rees DI. Medical marijuana laws, traffic fatalities, and alcohol consumption. J Law Econ. 2013;56:333-69.
14. Reece AS. Chronic toxicology of cannabis. Clinical Toxicology. 2009 Jul 1;47(6):517-24.
15. Hall W, Degenhardt L. The adverse health effects of chronic cannabis use.

Drug Test Anal. 2014;6(1-2):39-45.
16. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.
17. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction 2014;110:19-35.
18. Degenhardt L, Ferrari AJ, Calabria B, Hall WD, Norman RE, McGrath J, Flaxman AD, Engell RE, Freedman GD, Whiteford HA, Vos T. The global epidemiology and contribution of cannabis use and dependence to the global burden of disease: results from the GBD 2010 study. PLoS One. 2013;8(10):e76635.
19. Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug Alcohol Rev. 2010;29:318-30.
20. Imtiaz S, Shield KD, Roerecke M, Cheng J, Popova S, Kurdyak P, Fischer B, Rehm J. The burden of disease attributable to cannabis use in Canada in 2012. Addiction. 2015;111,653-662.
21. Fischer B, Imtiaz S, Rudzinski K, Rehm J. Crude estimates of cannabis-attributable mortality and morbidity in Canada-implications for public health focused intervention priorities. J Public Health. 2016;38(1):183-8.
22. Meier MH, Caspi A, Cerdá M, Hancox RJ, Harrington H, Houts R, Poulton R, Ramrakha S, Thomson WM, Moffitt TE. Associations between cannabis use and physical health problems in early midlife: a longitudinal comparison of persistent cannabis vs tobacco users. JAMA Psychiatry. 2016;73(7):731-740.
23. Bechtold J, Simpson T, White HR, Pardini, D. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. Psych Addictive Behav. Advance online publication. 2015;29(3):552-563.
24. Andreasson, S. Allebeck P. Cannabis and mortality among young men. Scandinavian J. Social Med. 1990; 18(1).
25. Fuster D, Cheng DM, Allensworth-Davies D, Palfai TP, Samet JH, Saitz R. No detectable association between frequency of marijuana use and health or healthcare utilization among primary care patients who screen positive for drug use. J Gen Intern Med 2014;29(1):133-9.
26. Sidney, S., et al. (1997). "Marijuana use and mortality." Am J Pub Health **87**(4): 585-590.
27. Gmel, Gerhard, et al. Alcohol and cannabis use as risk factors for injury–a case-crossover analysis in a Swiss hospital emergency department. BMC Public Health 9.1 (2009): 40.
28. Vidot, D. C., et al. (2014). "Emerging issues for our nation's health: the intersection of marijuana use and cardiometabolic disease risk." Journal of addictive diseases **33**(1): 1-8.
29. Ngueta G, Bélanger RE, Laouan-Sidi EA, Lucas M. *Cannabis* use in relation to obesity and insulin resistance in the Inuit population. Obesity. 2015;23:290-5.

30. Le Strat, Y. and B. Le Foll (2011). "Obesity and cannabis use: results from 2 representative national surveys." American Journal of Epidemiology **174**(8): 929-933.
31. Gregg, E. W. and J. E. Shaw (2017). Global Health Effects of Overweight and Obesity, Mass Medical Soc.
32. Haan, M. N. (2006). "Therapy Insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease." Nature Reviews. Neurology **2**(3): 159.
33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, and PRISMA-P group. Preferred reporting items for systematic review and meta-analysis protocols (Prisma-P) 2015 statement. Systematic Rev 2015; 4:1.
34. Kempker JA, Honig EG, Martin GS. The effects of marijuana exposure on expiratory airflow. A study of adults who participated in the U.S. National Health and Nutrition Examination Study. Ann Am Thorac Soc. 2015;12:135-41.
35. Centers for Disease Control. Deaths: Final data for 2013. Mortality Multiple Cause data files, Table 10. http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf (accessed 10/28/2015).
36. American Cancer Society. Cancer Facts and Figures 2013: http://www.cancer.org/research/cancerfactsfigures/cancerfactsfigures/cancer-facts-figures-2013
37. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct risk factor profiles for human papillomavirus type 16–positive and human papillomavirus type 16–negative head and neck cancers. J Nat Cancer Inst. 2008;100:407-20.
38. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, Woll PJ, Orlow I, Cox B, Brhane Y, Liu G. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. Int J Cancer. 2015;136:894-903.
39. Zhang Z-F, Morgenstern H, Spitz MR, Tashkin DP, Yu G-P, Marshall JR, et al. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev.1999;8:1071-8.
40. Efird JT, Friedman GD, Sidney S, Klatsky A, Habel LA, Udaltsova NV, et al. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. J Neurooncol. 2004;68:57-69.
41. Berthiller J, Straif K, Boniol M, Voirin N, Benhaim-Luzon V, Ben Ayoub W, Dari I, Laouamri S, Hamdi-Cherif M, Bartal M, Ben Ayed F, Sasco AJ. Cannabis smoking and risk of lung cancer in men. A pooled analysis of three studies in Magreb. J Thor Onc. 2008;3:1398- 1403.
42. Feng BJ, Khyatti M, Ben-Ayoub W, Dahmoul S, Ayad M, Maachi F, Bedadra W, Abdoun M, Mesli S, Bakkali H, Jalbout M. Cannabis, tobacco and domestic fumes intake are associated with nasopharyngeal carcinoma in North Africa. Brit J Cancer. 2009;101:1207-12.
43. Hsairi M, Achour N, Zouari B, Ben Romdhane H, Achour A, et al. Etiologic factors in primary bronchial carcinoma in Tunisia. La Tunise Medicale 1993;71:265-8.
44. Sasco AJ, Merrill RM, Dari I, Benhaim-Luzon V, Carriot F, Cann, CI, Bartal M. A case-

control study of lung cancer in Casablanca, Morocco. Cancer Causes Control 2002;13,609-616.
45. Voirin N, Berthiller J, Benhaïm-Luzon V, Boniol M, Straif K, Ayoub WB, Ayed FB, Sasco AJ. Risk of lung cancer and past use of cannabis in Tunisia. J Thorac Oncol 2006 Jul 31;1(6):577-9.
46. Chacko JA, Heiner JG, Siu W, Macy M, Terris MK. Association between marijuana use and transitional cell carcinoma. Urology 2006;67:100-4.
47. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang Z-F, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2006;15:1829-34.
48. Lacson JCA, Carroll JD, Tauzon E, Castelao EJ, Bernstein L, Cortessis VK. Population- based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer. 2012;118:5374-83.
49. Firth NA. Marijuana use and oral cancer: a review. Oral oncol. 1997;33:398-401.
50. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya KA. Squamous cell carcinoma of the oral cavity in patients aged 45 years and under: a descriptive analysis of 116 cases diagnosed in the South East of England from 1990 to 1997. Oral Oncol. 2003;39:106-14.
51. Sridhar KS, Raub WA, Weatherby NL, Metsch LR, Surratt HL, Inciardi JA, Duncan RC, Anwyl RS, McCoy CB. Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. J Psychoactive Drugs. 1994;26:285-8.
52. Chao C, Jacobson LP, Jenkins FJ, Tashkin D, Martínez-Maza O, Roth MD, Ng L, Margolick JB, Chmiel JS, Zhang ZF, Detels R. Recreational drug use and risk of Kaposi's sarcoma in HIV- and HHV-8- coinfected homosexual men. AIDS Res Hum Retrov 2009;25:149- 56.
53. Liang C, McClean MD, Marsit C, Christensen B, Peters E, Nelson HH, et al. A population- based case-control study of marijuana use and head and neck squamous cell carcinoma. Cancer Prev Res. 2009;2:759-68.
54. Llewellyn CD, Linklater K, Bell J, Johnson NW, Sarnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case control study. Oral Oncol. 2004;40:304-13.
55. Llewellyn CD, Johnson NW, Sarnakulasuriya S. Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case-control study in Southern England. Oral Path Med. 2004;33:525-32.
56. Sidney S, Quesenberry CP, Friedman GD. Marijuana use and cancer incidence (California, United States). Cancer Cause Control. 1997;8:722-8.
57. Maden C, Sherman KJ, Beckmann AM, Hislop TG, Teh CZ, Ashley RL, Daling JR. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. J Natl Cancer Inst. 1993;85:19-24.
58. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, *et al*.. Cannabis use

and risk of lung cancer: a case-control study. Eur Respir J. 2008,31:280-6.
59. Berthiller J, Yuan-chin AL, Boffetta P, Wei Q, Sturgis EM, Greenland S, et al. Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18:1544-51.
60. Callaghan RC, Allebeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Cause Control. 2013;24:1811-20.
61. Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. N Engl J Med 1987;317:973-7.
62. Daling JR, Doody DR, Xiaofei Sun BS, Trabert BL, Weiss NS, Chen C, et al.. Association of marijuana use and the incidence of testicular germ cell tumors. Cancer. 2009;115:1215-23.
63. Holly EA, Lele C, Bracci PM, McGrath MS. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. Am J Epidemiol. 1999;150:375-89.
64. Marks MA, Chaturvedi AK, Kelsey K, Straif K, Berthiller J, Schwartz SM, Smith E, Wyss A, Brennan P, Olshan AF, Wei Q. Association of marijuana smoking with oropharyngeal and oral tongue cancers: pooled analysis from the INHANCE consortium. Cancer Epidemiol Biomarkers Prev. 2014;23:160-71.
65. Nelson RA, Levine Am, Marks G, Bernstein L. Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma. Br J Cancer. 1997;76:1532-7.
66. Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. Cancer Res. 2004;64:4049-54
67. Thomas AA, Wallner LP, Quinn VP, Slezak J, Van Den Eeden SK, Chien GW, et al. Association between *Cannabis* use and the risk of bladder cancer: results from the California Men's Health Study. Urology. 2015;85:388-93
68. Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA. Marijuana Use and testicular germ cell tumors. Cancer. 2011;117:848-53.
69. Grubbs F. Procedures for detecting outlying observations in samples. Technometrics, 1969;11:1-21.
70. Guzmán M. Cannabinoids: potential anticancer agents. Nat Rev Cancer 2003,3:745-755.
71. Galve-Roperh I, Sánchez C, Cortéz ML, Gómez del Pulgar T, Izquierdo M, Guzmán M. Anti-tumoral action of cannabinoids: Involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. Nat Med. 2000;6:313-9.
72. Guzman, M., et al. (2006). "A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme." British journal of cancer **95**(2): 197.
73. Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev 2006;27(1):73-100.
74. Roglic G, Unwin N. Mortality attributable to diabetes: estimates for the year 2010. Diabetes

Res Clin Pr 2010;87(1):15-9.
75. American Diabetes Association. Economic costs of diabetes in the US in 2007. Diabetes care. 2008;31(3):596-615.
76. Rajavashisth TB, Shaheen M, Norris KC, Pan D, Sinha SK, Ortega J, et al. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National health and Nutrition Examination Survey (NHANES) III. BMJ Open. 2012;2:e000494.
77. Le Foll, B., et al. (2013). "Cannabis and Δ 9-tetrahydrocannabinol (THC) for weight loss?" Medical hypotheses **80**(5): 564-567.
78. Alshaarawy O, Anthony JC. Cannabis smoking and diabetes mellitus: results from meta-analysis with eight independent replication samples. Epidemiology. 2015;26:597-600.
79. Carracedo, Arkaitz, et al. "Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress–related genes." *Cancer research* 66.13 (2006): 6748-6755.
80. Cianchi, Fabio, et al. "Cannabinoid Receptor Activation Induces Apoptosis through Tumor Necrosis Factor α–Mediated Ceramide De novo Synthesis in Colon Cancer Cells." *Clinical Cancer Research* 14.23 (2008): 7691-7700.
81. Dando, I., et al. "Cannabinoids inhibit energetic metabolism and induce AMPK-dependent autophagy in pancreatic cancer cells." *Cell death & disease* 4.6 (2013): e664.
82. Donadelli, M., et al. "Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism." *Cell death & disease* 2.4 (2011): e152.
83. Qamri, Zahida, et al. "Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer." *Molecular cancer therapeutics* 8.11 (2009): 3117-3129.
84. Olea-Herrero, N., et al. "Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R (+)-Methanandamide and JWH-015: involvement of CB2." *British journal of cancer* 101.6 (2009): 940-950.
85. Saghafi, Negin, David K. Lam, and Brian L. Schmidt. "Cannabinoids attenuate cancer pain and proliferation in a mouse model." *Neuroscience letters* 488.3 (2011): 247-251.
86. Sreevalsan, Sandeep, et al. "Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent." *Anticancer research* 31.11 (2011): 3799-3807.
87. Casanova, M. L., et al. (2003). "Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors." Journal of Clinical Investigation **111**(1): 43.
88. Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. Cannabis in palliative medicine: improving care and reducing opioid-related morbidity. Am J Hosp Palliat Care. 2011;28(5):297-303.
89. Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. Oncotarget. 2014;5(15):5852.
90. Ostadhadi S, Rahmatollahi M, Dehpour AR, Rahimian R. Therapeutic potential of cannabinoids in counteracting chemotherapy-induced adverse effects: an exploratory review. Phytother Res 2015;29(3):332-8.

91. Huang YH, Zhang ZF, Tashkin DP, Feng B, Straif K, Hashibe M. An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiol Biomarkers Prev. 2015;24:15-31.
92. de Carvalho MF, Dourado MR, Fernandes IB, Araújo CT, Mesquita AT, Ramos-Jorge ML. Head and neck cancer among marijuana users: A meta-analysis of matched case–control studies. Arch Oral Biol 2015;60(12):1750-5.
93. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. New Engl J Med. 2003;348:1625-38.
94. Lontchi-Yimagou, E., et al. (2013). "Diabetes mellitus and inflammation." Current diabetes reports **13**(3): 435-444.
95. Penner EA, Buettner H, Mittleman MA. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am J Med. 2013;126:583-9.
96. Carrieri MP, Serfaty L, Vilotitch A, Winnock M, Poizot-Martin I, Loko MA, Lions C, Lascoux-Combe C, Roux P, Salmon-Ceron D, Spire B. Cannabis use and reduced risk of insulin resistance in hiv-hcv infected patients: a longitudinal analysis (ANRS CO13 HEPAVIH). Clin Infect Dis 2015;61(1):40-8.
97. Muniyappa R, Sable S, Ouwerkerk R, Mari A, Gharib AM, Walter M, Courville A, Hall G, Chen KY, Volkow ND, Kunos G. Metabolic effects of chronic cannabis smoking. Diabetes Care. 2013;36:2415-22.
98. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). Am J Cardiol. 2006;98:478-484.
99. Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, Gallily R. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmunity. 2006;39(2):143- 51.
100. Weiss L, Zeira M, Reich S, Slavis S, Raz I, Mechoulam R et al. Cannabidiol arrests onset of autoimmune diabetes in NOD mice. Neuropharmacol. 2008;54:244-9.
101. Gallant M, Odei-Addo F, Frost CL, Levendal RA. Biological effects of THC and a lipophilic cannabis extract on normal and insulin resistant 3T3-L1 adipocytes. Phytomedicine. 2009;16:942-9.
102. Rajesh M, Mukhopadhyay P, Bátkai S, Patel V, Saito K, Matsumoto S, Kashiwaya Y, Horváth B, Mukhopadhyay B, Becker L, Haskó G. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. J Am Col Cardiol 2010;56:2115-25.
103. Rajesh M, Mukhopadhyay P, Bátkai S, Haskó G, Liaudet L, Drel VR, Obrosova IG, Pacher
P. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. Am J Physiol – Heart C. 2007;293:H610-9.
104. Comelli F, Bettoni I, Colleoni M, Giagnoni G, Costa B. Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress.

Phytotherapy Res. 2009;23(12):1678-84.
105. Haroutounian S., Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, Davidson E. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain. Clin J Pain 2016;32,1036-1043.
106. Centers for Disease Control. National Diabetes Statistics Report, 2014. http://www.cdc.gov/diabetes/pdfs/data/2014-report-estimates-of-diabetes-and-its- burden-in-the-united-states.pdf
107. Hempstead K. The accuracy of a death certificate checkbox for diabetes: early results from New Jersey. Public Health Rep 2009;124:726-732.
108. McEwen LN, Kim C, Haan M, Ghosh D, Lantz PM, Mangione CM, Safford MM, Marrero D, Thompson TJ, Herman WH. Diabetes reporting as a cause of death results from the Translating Research Into Action for Diabetes (TRIAD) study. Diabetes Care. 2006;29:247-53.
109. Franz CA, Frishman WH. Marijuana Use and Cardiovascular Disease. Cardiol Rev. 2016;24(4):158-62.
110. Sidney S. Cardiovascular consequences of marijuana use. J Clin Pharmacol 2002;42:64S-70S.
111. Reis, Jared P., et al. "Cumulative Lifetime Marijuana Use and Incident Cardiovascular Disease in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study." *American journal of public health* 107.4 (2017): 601-606.
112. Rumalla, Kavelin, Adithi Y. Reddy, and Manoj K. Mittal. Recreational marijuana use and acute ischemic stroke: a population-based analysis of hospitalized patients in the United States. *Journal of the neurological sciences* 364 (2016): 191-196.
113. Aryana A, Williams MA. Marijuana as a trigger of cardiovascular events: speculation or scientific certainty? Int J Cardiol. 2007;118:141-4.
114. Bachs L, Mørland H. Acute cardiovascular fatalities following cannabis use. Forensic Sci Int. 2001;124:200-3.
115. Barber PA, Pridmore HM, Krishnamurthy V, Roberts S, Spriggs DA, Carter KN, et al. Cannabis, ischemic stroke, and transient ischemic attack. A case-control study. J Am Heart Assoc Stroke. 2013;44:2317-29.
116. Hackam DG. Cannabis and stroke. Systematic appraisal of case reports. J Am Heart Assoc Stroke. 2015;46:852-6.
117. Hartung B, Kauferstein S, Ritz-Timme S, Daldrup T. Sudden unexpected death under acute influence of cannabis. Forensic Sci Int. 2014;237:e11-3.
118. Jouanjus E, Lapeyre-Mestre M, Micallef J. Cannabis use: signal of increasing risk of serious cardiovascular disorders. J Am Heart Assoc. 2014;3:e000638
119. Lindsay AC, Foale RA, Warren O, Henry JA. Cannabis as a precipitant of cardiovascular emergencies. Int J Cardiol. 2005;104:230-2.
120. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial

infarction by marijuana. Circulation. 2001;103:2805-9.
121. Mouzak A, Agathos P, Kerezoudi E, Mantas A, Vourdeli-Yiannakoura E. Transient ischemic attack in heavy cannabis smokers–how 'safe' is it? Eur Neurol. 2000;44:42-4.
122. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol. 2014;113:187-90.
123. Pratap B, Korniyenko A. Toxic effects of marijuana on the cardiovascular system. Cardiovasc Toxicol. 2012;12:143-8.
124. Moussouttas M. Cannabis use and cerebrovascular disease. Neurologist. 2004;10(1):47-53.
125. Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman MA. Marijuana use and long-term mortality among survivors of acute myocardial infarction. Am Heart J. 2013;165:170-5.
126. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. Am Heart J. 2008;155:465-70.
127. Steffens S, Veillard NR, Arnaud C, Pelli G, Burger F, Staub C et al. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. Nature 2005;434: 782-6.
128. De Petrocellis L, Melck D, Bisogno T, Di Marzo V. Endocannabinoids and fatty acid amides in cancer, inflammation and related disorders. Chem Phys Lipids. 2000;108:191-209.
129. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105, 1135-1143.
130. Singla S, Sachdeva R, Mehta JL. Cannabinoids and atherosclerotic coronary heart disease. Clin Cardiol. 2012;35:329-35.
131. Durst R, Dananberg H, Gallily R, Mechoulam R, Meir K, Grad E, Beeri R, Pugatsch T, Tarsish E, and Lotan C. Cannabidiol, a nonpsychoactive *Cannabis* constituent, protects against myocardial ischemic reperfusion injury. Am J Physiol Heart Circ Physiol 2007; 293:H3602-H3607.
132. Rantakömi SH, Kurl S, Sivenius J, Kauhanen J., Laukkanen JA. The frequency of alcohol consumption is associated with the stroke mortality. Acta Neurol Scand. 2014;DOI:10.1111/ane.12243
133. Fosbøl, Emil Loldrup, et al. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. *Circulation: Cardiovascular Quality and Outcomes* 3.4 (2010): 395-405.
134. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine. A population-based study of hospitalized patients. Arch Gen Psychiat. 2007;64:495-502.
135. Jones RT. Cardiovascular system effects of marijuana. J Clin Pharmacol. 2002;42(S1):58S-

63S.
136. Frishman WH, Del Vecchio A, Sanal S, Ismail A. Cardiovascular manifestations of substance abuse: part 2: alcohol, amphetamines, heroin, cannabis, and caffeine. Heart Dis. 2002;5:253-71.
137. Melamede R. Cannabis and tobacco smoke are not equally carcinogenic. Harm Reduction Journal 2005:2(1):1.
138. Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA. The association between marijuana smoking and lung cancer: a systematic review. Arch Intern Med. 2006;166:1359-67.
139. Tashkin DP. Effects of marijuana smoking on the lung. Ann Am Thorac Soc. 2013;10:239-47.
140. Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR, McLachlan CR, Greene JM, Moffitt TE, Caspi A, Sears MR. Effects of cannabis on lung function: a population-based cohort study. Eur Respir J. 2010;35:42-7.
141. Joshi M, Joshi A, Bartter T. Marijuana and lung diseases. Curr Opin Pulm Med. 2014;20(2):173-9.
142. Beshay M, Kaiser H, Niedhart D, Reymond MA, Schmid RA. Emphysema and secondary pneumothorax in young adults smoking cannabis. Eur J Cardio-Thorac. 2007;32:834-8.
143. Fiorelli A, Accardo M, Vicidomini G, Messina G, Laperuta P, Santini M. Does cannabis smoking predispose to lung bulla formation? Asian Cardiovasc Thorac Ann. 2013;0218492313478954.
144. Gill A. Bong lung: Regular smokers of cannabis show relatively distinctive histologic changes that predispose to pneumothorax. Am J Surg Pathol. 2005;29:980-2.
145. Tan C, Hatam N, Treasure T. Bullous disease of the lung and cannabis smoking: insufficient evidence for a causative link. J Royal Soc Med. 2006;99:77-80.
146. Lee MH, Hancox RJ. Effects of smoking cannabis on lung function. Expert Rev Resp Med. 2014;5,537-547.
147. Vethanayagam D, Saad E, Yehya J. Aspergillosis spores and medical marijuana. CMAJ. 2016;188(3):217.
148. Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest. 1988;94(2):432-3.
149. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. Harm Reduction J. 2007;16;4:11, DOI**:** 10.1186/1477-7517-4-11.
150. Tan WC, Lo C, Jong A, Xing L, FitzGerald MJ, Vollmer WM, Buist SA, Sin DD, Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group. Marijuana and chronic obstructive lung disease: a population-based study. CMAJ. 2009;180:814-20.
151. Parfieniuk A, Flisiak R. Role of cannabinoids in chronic liver diseases. World J Gastroenterol. 2008;14(40):6109-14.
152. Purohit V, Rapaka R, Shurtleff D. Role of cannabinoids in the development of fatty liver

(steatosis). AAPS J. 2010;12(2):233-7.
153. Loterztajn S, Teixeira-Clerc F, Julien B, Deveaux V, Ichigotani Y, Manin S, Tran-Van-Nhieu J, Karsak M, Zimmer A, Mallat A. CB2 receptors as new therapeutic targets for liver diseases. Brit J Pharmacol 2008;153:286-289.
154. Hézode C, Roudot-Thoraval F, Nguyen S, Grenard P, Julien B, Zafrani ES, Pawlostky JM, Dhumeaux D, Lotersztajn S, Mallat A. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatol. 2005;42(1):63-71.
155. Ishida JH, Peters MG, Jin C, Louie K, Tan V, Bacchetti P, Terrault NA. Influence of cannabis use on severity of hepatitis C disease. Clin Gastroenterol Hepatol. 2008;6:69- 75.
156. Hézode C, Zafrani ES, Roudot–Thoraval F, Costentin C, Hessami A, Bouvier–Alias M, Medkour F, Pawlostky JM, Lotersztajn S, Mallat A. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenterol. 2008;134(2):432-9.
157. Brunet L, Moodie EE, Rollet K, Cooper C, Walmsley S, Potter M, Klein MB, Canadian Co-infection Cohort Investigators. Marijuana smoking does not accelerate progression of liver disease in HIV–hepatitis C coinfection: a longitudinal cohort analysis. Clin Infect Dis. 2013;57:663-70.
158. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013;309:657-659.
159. Petta S, Muratore C, Craxi A. Non-alcoholic fatty liver disease pathogenesis: the present and the future. Dig Liver Dis. 2009;41:615-25.
160. Schreuder TC, Verwer BJ, van Nieuwkerk CM, Mulder CJ. Nonalcoholic fatty liver disease: an overview of current insights in pathogenesis, diagnosis and treatment. World J Gastroenterol. 2008;14:2474.
161. Biegon A. Cannabinoids as neuroprotective agents in traumatic brain injury. Current pharmaceutical design. 2004;10(18):2177-83.
162. Pazos MR, Cinquina V, Gomez A, Layunta R, Santos M, Fernández-Ruiz J, Martínez-Orgado J. Cannabidiol administration after hypoxia–ischemia to newborn rats reduces long-term brain injury and restores neurobehavioral function. Neuropharmacology. 2012;63(5):776-83.
163. Louw DF, Yang FW, Sutherland GR. The effect of δ-9-tetrahydrocannabinol on forebrain ischemia in rat. Brain Res. 2000;857(1):183-7.
164. Touriño C, Zimmer A, Valverde O. THC prevents MDMA neurotoxicity in mice. Plos One. 2010;5:e9143.
165. Castelli MP, Madeddu C, Casti A, Casu A, Casti P, Scherma M, Fattore L, Fadda P, Ennas MG. Δ9-tetrahydrocannabinol prevents methamphetamine-induced neurotoxicity. PloS one. 2014;9(5):e98079.
166. Jacobus J, McQueeny T, Bava S, Schweinsburg BC, Frank LR, Yang TE, Tapert SF. White matter integrity in adolescents with histories of marijuana use and binge drinking.

Neurotoxicology and teratology. 2009 Dec 31;31(6):349-55.
167. Nguyen BM, Kim D, Bricker S, Bongard F, Neville A, Putnam B, Smith J, Plurad D. Effect of marijuana use on outcomes in traumatic brain injury. Am Surg. 2014;80:979-83.
168. O'Phelan K, McArthur DL, Chang CW, Green D, Hovda DA. The impact of substance abuse on mortality in patients with severe traumatic brain injury. J Trauma. 2008;65:674- 7.
169. Knoller N, Levi L, Shoshan I, Reichenthal E, Razon N, Rappaport ZH, Biegon A. Dexanabinol (HU-211) in the treatment of severe closed head injury: A randomized, placebo-controlled, phase II clinical trial. Crit Care Med. 2002;30:548-54.
170. Pazos MR, Cinquina V, Gomez A, Layunta R, Santos M, Fernández-Ruiz J, Martínez-Orgado J. Cannabidiol administration after hypoxia–ischemia to newborn rats reduces long-term brain injury and restores neurobehavioral function. Neuropharmacology. 2012;63:776-83.
171. Panikashvili D, Simeonidou C, Ben-Shabat S, Hanuš L, Breuer A, Mechoulam R, Shohami E. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature. 2001;413(6855):527-31.
172. Hartung B, Schwender H, Roth EH, Hellen F, Mindiashvili N, Rickert A, Ritz-Timme S, Grieser A, Monticelli F, Daldrup T. The effect of Cannabis on regular Cannabis consumer's ability to ride a bicycle. Int J Leg Med. 2016;DOI 10.1007/s00414-015-1307- y
173. Kolakowsky-Hayner SA, Gourley III EV, Kreutzer JH, Marwitz DX, McKinley SA. Pre-injury substance abuse among persons with brain injury and persons with spinal cord injury. Brain Injury. 1999;13(8):571-81.
174. Tait RJ, Anstey KJ, Butterworth P. Incidence of self-reported brain injury and the relationship with substance abuse: findings from a longitudinal community survey. BMC Public Health 2010;10.1:1.
175. Ilie G, Boak A, Adlaf EM, Asbridge M, Cusimano MD. Prevalence and correlates of traumatic brain injuries among adolescents. JAMA. 2013;309:2550-2.
176. Gerberich SG, Sidney S, Braun BL, Tekawa IS, Tolan KK, Quesenberry CP. Marijuana use and injury events resulting in hospitalization. Ann Epidemiol. 2003;13(4):230-7.
177. Compton, RP, and Berning A. Drug and Alcohol Crash Risk. NHTSA'S Office of Behavioral Safety Research 2015;DOT HS 812 117, http://www.nhtsa.gov/staticfiles/nti/pdf/812117- Drug_and_Alcohol_Crash_Risk.pdf
178. Morris RG, TenEyck M, Barnes JC, Kovandzic TV. The effect of medical marijuana laws on crime: evidence from state panel data, 1990-2006. PloS one. 2014;9(3):e92816.
179. Agosti V, Nunes E, Levin F. Rates of psychiatric comorbidity among U.S. residents with lifetime *Cannabis* dependence. Am J Drug and Alcohol Abuse. 2002;28:643-652.
180. Goodwin RS, Darwin WD, Chiang CN, et al. Urinary elimination of 11-nor-9-tetrahydrocannabinol in cannabis users during continuously monitored abstinence. J Anal Toxicol. 2008;32:562-9.
181. Eubanks LM, Rogers CJ, Beuscher IV AE, Koob GF, Olson AJ, Dickerson TJ, Janda KD. A

molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharmeceut. 2006;3:773-7.
182. Ramírez BG, Blázquez C, Gómez del Pulgar T, Guzmán M, de Ceballos ML Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. J Neurosci. 2005;25:1904-13.
183. Sagredo O, Pazos MR, Satta V, Ramos JA, Pertwee RG, Fernández-Ruiz J. Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease. J Neurosci Res. 2011;89:1509-18.
184. Olmos-Alonso A, Schetters ST, Sri S, Askew K, Mancuso R, Vargas-Caballero M, Holscher C, Perry VH, Gomez-Nicola D. Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology. Brain. 2016;139(3):891-907.
185. Fagan SG, Campbell VA. The influence of cannabinoids on generic traits of neurodegeneration. Brit J Pharmacol. 2014;171(6):1347-60.
186. Currais A, Quehenberger O, Armando AM, Daugherty D, Maher P, Schubert D. Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids. NPJ Aging Mech Dis. 2016;2:16012.
187. Marchalant Y, Brothers HM, Norman GJ, Karelina K, DeVries AC, Wenk GL. Cannabinoids attenuate the effects of aging upon neuroinflammation and neurogenesis. Neurobiol Dis. 2009;34(2):300-7.
188. Bilkei-Gorzo A, Albayram O, Draffehn A, Michel K, Piyanova A, Oppenheimer H, Dvir-Ginzberg M, Rácz I, Ulas T, Imbeault S, Bab I. A chronic low dose of (1) 9-tetrahydrocannabinol (THC) restores cognitive function in old mice. Nature Medicine. 2017 May 8.
189. Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, Miller I, Flamini R, Wilfong A, Filloux F, Wong M, Tilton N, Bruno P, Bluvstein J, Hedlund J, Kamens R, Maclean J, Nangia S, Singhal NS, Wilson CA, Patel A, Cilio MR. Cannabidiol in patients with treatment-resistant epilepsy: an open label interventional trial. Lancet Neurol. 2015;15(3):270-278.
190. James BD, Leurgans SE, Hebert LE, Scherr PA, Yaffe K, Bennett DA. Contribution of Alzheimer disease to mortality in the United States. Neurology. 2014,82:1045-1050.
191. Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpää M, Tomson T. Mortality of epilepsy in developed countries: a review. Epilepsia. 2005;46(s11):18-27.
192. Bachhuber MA, Saloner B., Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med. 2014;174:1668-73.
193. National Institute on Alcohol Abuse and Alcoholism. Alcohol facts and statistics. http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts- and-statistics (accessed 10/29/2015)
194. Lynch ME, Clark AJ. Cannabis reduces opioid dose in the treatment of chronic non-cancer

pain. J Pain Symptom Manag. 2003;25(6):496-8.
195. Boehnke KF, Litinas E, Clauw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain. 2016;17(6):739-44.
196. Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. Cannabis in palliative medicine: improving care and reducing opioid-related morbidity. Am J Hospice Palliative Med. 2011;1049909111402318.
197. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. Drug Alc Dep 2017;173:144-150.
198. Reiman A. Cannabis as a substitute for alcohol and other drugs. Harm Reduct J. 2009;6: 35. doi:10.1186/1477-7517-6-35.
199. Nunberg H, Kilmer B, Pacula R, Burgdorf J. An analysis of applicants presenting to a medical marijuana specialty practice in California. J Drug Policy Anal. 2011; 4, 1.
200. Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction. 2004;99:686-696.
201. Lachenmeier DW, Rehm J. Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. Sci Rep. 2015;5:8126. DOI: 10.1038/srep08126
202. National Council on Alcoholism and Drug Dependence. https://ncadd.org/about-addiction/alcohol-drugs-and-crime (accessed 1/20/2016)
203. Guttmannova K, Lee CM, Kilmer JR, Fleming CB, Rhew IC, Kosterman R, Larimer ME. Impacts of changing marijuana policies on alcohol use in the United States. Alcohol Clin Exp Res. 2016;40(1):33-46.
204. Allsop DJ, Dunlop AJ, Sadler C, Rivas GR, McGregor IS, Copeland J. Changes in cigarette and alcohol use during cannabis abstinence. Drug Alcohol Depen. 2014;138:54-60.
205. Weinberger AH, Platt J, Goodwin RD. Is cannabis use associated with an increased risk of onset and persistence of alcohol use disorders? A three-year prospective study among adults in the United States. Drug Alcohol Depend. 2016;161:363-7.
206. Sewell RA, Poling J, Sofuoglu M. The effect of cannabis compared with alcohol on driving. Am J Addiction. 2009;18(3):185-93.
207. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ. 2012 Feb 9;344:e536.
208. Elvik R. Risk of Road Accident Associated with the Use of Drugs: A systematic review and meta-analysis of evidence from epidemiological studies. Accid Anal Prev. 2013;60:254– 67.
209. Li MC, Brady JE, DiMaggio CJ, Lusardi AR, Tzong KY, Li G. Marijuana use and motor vehicle crashes. Epidemiol Rev. 2012;34:65-72.
210. Fergusson DM, Horwood LJ. Cannabis use and traffic accidents in a birth cohort of young

adults. Accident Anal Prev. 2001;33:703-11.
211. Santaella-Tenorio J, Mauro CM, Wall MM, Kim JH, Cerdá M, Keyes KM, Hasin DS, Galea S, Martins SS. US Traffic Fatalities, 1985–2014, and Their Relationship to Medical Marijuana Laws. American journal of public health. 2017 Feb;107(2):336-42.
212. Balko, R. Since marijuana legalization, highway fatalities in Colorado are at near-historic lows. The Washington Post, Aug. 5, 2014.
213. Couper FJ, Peterson BL. The prevalence of marijuana in suspected impaired driving cases in Washington state. J Analytical Toxicol. 2014;38(8):569-74.
214. Salomonsen-Sautel S, Min SJ, Sakai JT, Thurstone C, Hopfer C. Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. Drug Alcohol Depen. 2014;140:137-44.
215. Subbaraman MS. Substitution and complementarity of alcohol and Cannabis: a review of the literature. Subst Use Misuse. 2016;51(11):1399-414.
216. Centers for Disease Control and Prevention. Injury Prevention and Control: motor vehicle safety. http://www.cdc.gov/motorvehiclesafety/impaired_driving/impaired-drv_factsheet.html
217. Anderson DM, Rees DI, and Sabia JJ. Medical marijuana laws and suicides by gender and age. Am J Public Health. 2014;104:2369-76.
218. Grucza RA, Hur M, Agrawal A, Krauss MJ, Plunk AD, Cavazos-Rehg PA, Chaloupka FJ, Bierut LJ. A reexamination of medical marijuana policies in relation to suicide risk. Drug Alcohol Depen. 2015;152:68-72.
219. Grucza RA, Hur M, Agrawal A, Krauss MJ, Plunk AD, Cavazos-Rehg PA, Chaloupka FJ, Bierut LJ. Medical marijuana laws and suicide. Am J Public Health. 2015;105(8):e3-
220. National Institute on Drug Abuse. National Survey of Drug Use and Health. https://www.drugabuse.gov/national-survey-drug-use-health, accessed 10/28/2015.
221. Gurney J, Shaw C, Stanley J, Signal V, Sarfati D. Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC cancer. 2015;15(1):1.
222. Kuper H, Boffetta P, Adami HO. Tobacco use and cancer causation: association by tumour type. Journal Intern Med 2002;252(3):206-24.
223. Alexander M (2011). *The New Jim Crow.* New York, NY: New Press.
224. Hari J (2015). *Chasing the scream: The first and last days of the war on drugs* (First U.S. edition.). New York, New York: Bloomsbury.

Dr. Ian Jacobs

Ganja Thoughts, for Commission

New Area: All must be up for Regular Review

Decriminalization

Proven Medical Uses

Preventing Harm to Children & Adolescents

A. New Area: All must be up for Regular Review

No One has all the truths here, and even those will change as time progresses. As we move forward there needs to be planned regular review of our position, which bearing in mind our small population size must be based on wide international experience that is culturally appropriate and scientifically supported. Anecdotal, local or otherwise cannot be the basis of any position

B. Decriminalization essential

Class & historical based bias against marijuana use (e.g. vis-a- vis alcohol and tobacco, which do much more harm to our society) and its consequent criminalization of large segments of our youth must stop. International and regional experience, as well as local knowledge will be needed to guide. Given our extremely small sample size, to rely on local anecdotal 'evidence' would be fool-hardy. Local stadards and regukations will be needed re:

1. Maximum weight of Marijuana allowed for personal use
2. Maximum Number of plants allowed in your property
3. Registration of farming, transport and sale (which must allow for small sellers)
4. Control of strength of varieties used
5. Outlawing of synthetic marijuana (we do not have testing and monitoring resources to facilitate this)
6. Measures to prevent/minimise cutting of Marijauna with impurities, or cocaine or other drugs
7. Use in public spaces

C. Medical Use

Use of appropiate formulations of marijuana for conditions local parctitioner board (medical/civil/rastafarian/lay) deem proven scientifically regionally or internationally. Caribbean, African and European and North American sources to be used) List will be long and must be subljject to at least biennial review. My immediate reccommendations would be Glaucoma, Chronic Pain, Severe Epilepsy in Children (? Adults); Incurable Cancer. Evidence for various psychiatric uses should be evaluated during initial formulation of any legislation

D. Protection of Children and Adolescents

With de-criminalization, marijuana will become increasingly available. The evidence on the effect of this on adolescent use is variable. Current evidence for the potential of damage to developing brains seems compelling, and we would be foolish to disregard this. Serious public Ed program needed here, but should NOT unduly delay/ be used as an excuse for delaying de-criminalzation.

1. Use of by persons under 18 should be prohibited. Evidence suggests that marijuana can have deliterious

effects on the developing brain up to age 25 years, but by 18 yrs we should have provided enough public education to enable youth to make their own determinations, as they d on Alcohol and tobacco.

2. Sale to such persons by those over the age of 18, or by their Minor agents should be liable to prosecution and jail time
3. Need to get effective buy in from de-criminalalization advocates on this. The dangers of tobacco and alcohol use to children and adolescents was recognized only after centuries.

Many persons are fearful of de-criminalization, even to the modest extent suggested above. We must realise that this represents the effects of years of cultural conditioning. The harm done by Tobacco and Alcohol to our nation outweighs by far any potential damage by marijuana. The societal gains (freeing up police for more serious matters, avoiding criminalizing youth) of de-criminalization are significant and must be embraced, and not with an over-abundance of caution. There is a considerable body of evidence to support this, most strikingly that the societies of Portugal and the Netherlands have continued to thrive after decades of de-criminalization.

Organisation of Rastafari in Unity (ORU)

Rastafari Position Paper on the Hola Herb (Cannabis)

November, 2018

This submission has been informed by years of reasoning among elders, brethrens and sistrens, public sensitization in the form of town hall, meetings and panel discussions with relevant stakeholders. It is also well informed by research into the historical and cultural activities of our ancestors.

The Organisation of Rastafari in Unity (ORU), is a National umbrella organization of Rastafari in both St. Kitts and Nevis and as such I an I can proudly say that the views expressed represent a vast majority of the Rastafari community.

Rastafari is a very well established religious/spiritual lifestyle within St. Kitts /Nevis, throughout the region and in fact throughout the entire world. It is also a well-established fact that Rastafari over the years has endured physical and psychological brutality and criminalization for its entrepreneurial, sacramental, cultural, medicinal and recreational uses of cannabis/ganja.

The use of the herb is a basic human right and also a religious/spiritual right. Such is well documented within our constitution.

Rastafari claim/report that the current governmental policy with regards to the enforcement of the Drugs (Prevention and Abatement of the Misuse and Abuse of Drugs) Act hinders our ability to enjoy our freedom of conscience and religion. The current enforcement practices have had an adverse impact upon membership, recruitment efforts, religious gatherings, business practices and the destabilization of the family structure.

Rastafari has been increasingly marginalized in the exercise of their cultural and religious rights leading to a life of poverty, disease and illiteracy; thus being vulnerable to the social ills that affect the general population.

Any amendments or changes to the management of ganja in St. Kitts/Nevis must provide for the opportunity to compensate the Rastafari community for the atrocities endured. The State can take the following welcomed and important reparatory justice steps which should include, but are not limited to:

- Legal recognition of the RastafarI faith to combat religious intolerance;
- Train law enforcement/judicial personnel to respect the cultural mores of groups such as RastafarI and use appropriate interface strategies;
- Expunge the records of persons convicted of possession of small amounts of cannabis. This would assist those affected to reintegrate into the economy and society of St. Kitts and Nevis;

- Facilitate social rehabilitation of persons using ganja who were given the option to claim addiction, in order to avoid prosecution, and be committed to the psychiatric and other institutions;
- Apologize and provide remedies to the families of persons who have been institutionalized in any way due to their use of ganja;
- Allocate strategic designated spaces with appropriate business infrastructure for the operation of business enterprises by RastafarI;
- Disburse an annual percentage (10%) of taxes collected from the ganja trade to the RastafarI community, through its Mansions and registered organisations, for its socio-economic development;

1. Economic stake includes, but are not limited to:
    - Cultivation, storage, processing and marketing locally and internationally;
    - Sovereignty over ganja seeds – the rights to propagate, store, distribute and register specialty strains/local seeds;
    - Registration of individual and collective brand ownership of various strains of cannabis;
    - Registration of production, processing and marketing cooperatives;
    - Access, individually and collectively, to industry incentives;
    - Investment and expansion of ganja trading activity and ownership into value added products and services;
    - Protection of Rastafari intellectual property rights to its Traditional and Indigenous Knowledge of ganja;
    - Any other such rights as may pertain to trade in ganja in local and foreign markets.
2. Cultural stake that should include, but not be limited to:
    - Recognize and uphold the natural relationship between Rastafari and cannabis sativa from its inception in St. Kitts/Nevis in the early 1970's.
    - Freedom to grow unlimited ganja around RastafarI homes/residences, backyards and communal grounds;
    - Individual home and community usage for medicinal, culinary, cosmetic, esthetic, customary and recreational purposes;
    - Creative and artistic expression such as carving, ornaments, jewelry, and functional objects made from all parts of the ganja plant;
    - Use at public events/activities organized by RastafarI such as family days, marches, rallies, motorcades; training sessions, fund raisers, exhibitions, celebration of historical dates and events etc.
3. Sacramental stake includes
    - Possession, control and use of unrestricted amounts of ganja at RastafarI homes and in collective spiritual spaces, namely Tabernacles, Headquarters, Temples, Camps; Nyahbinghi, Reasonings, Rites of Passage - Sanctification of newborns, Initiation of adolescents, marriages, transitions ceremonies;
4. Social Stake includes
    - Usage as communal currency for bartering of goods and services.

Suggestions:

The following are suggestions that should be incorporated into the Drugs (Prevention and Abatement of the Misuse and Abuse of Drugs) Act of St. Kitts/Nevis.

5. The revised Drug Act should provide for the possession and smoking of ganja, use of ganja by persons of the Rastafarian faith, and use of ganja for medicinal, therapeutic, scientific and recreational purposes.

Possession of Ganja

6. Possession of 4 ounces ganja is no longer an offence for which one can be arrested, charged and have to go to court, and it will not result in a criminal record or fine.
7. Possession of ganja for religious purposes as a sacrament in adherence to a particular faith
8. Possession of ganja for medicinal or therapeutic purposes as recommended or prescribed by a registered medical doctor or other health practitioner including herbal doctors, nutritionists, chiropractors etc… approved by the Minister of Health.
9. Possession of ganja for purposes of scientific research that is conducted by an accredited institution
10. Possession of ganja at an exempt event of Rastafari.
11. Possession of ganja pursuant to a licence, authorization or permit issued by the government.

Smoking of Ganja

12. Smoking of ganja in a public place or within five metres of a public place is prohibited in a manner similar to cigarettes.
13. A person who smokes in public cannot be arrested or detained.
14. Smoking of ganja at privately-occupied residences that are not used for commercial purposes is not an offence.
15. Furthermore, smoking of ganja will be legally permitted in places that are licensed for the smoking of ganja for medical or therapeutic purposes. Adherents of the Rastafarian faith will also be permitted to smoke/use ganja for sacramental, medicinal and recreational purposes in places of Rastafarian worship or gatherings.

Medicine and Healing

16. A person who is suffering from cancer or any other terminal or serious chronic illness may import medicine or a therapeutic product derived from or containing ganja. In order to do so, a registered medical practitioner or recognized herbal doctor must certify that the person is suffering from the illness, and must recommend the person's use of the medicine or therapeutic product. Rastafari is permitted to use ganja in a lifestyle of preventative medicine.
17. Administration to others should not have this frantic approach and the right should not be solely given to medical practitioners. Indigenous medicines have been concocted and distributed by bush doctors, herbalists and other leaders in a community. One should have the right to administer to another with choice and consent.

18. Administration to children should solely be the right of the parents and full consent from parents.
19. Preference must be given to local producers to satisfy the demand. Importation should be a last resort.

Cultivation for scientific research

20. An accredited institution or other body may apply for authorization to cultivate ganja in furtherance of scientific research, on lands approved for that cultivation.
21. An authorization to cultivate ganja for research purposes also protects any third party who is engaged by the scientific institution or body for this purpose.
22. Local growers must be given the opportunity to satisfy this demand before any ganja be allowed to be imported.

Cultivation to Supply Dispensaries

23. Individuals can apply for authorization to cultivate ganja.

Cultivation for Rastafarian sacramental purposes

24. Persons who are adherents to the Rastafarian faith, or Rastafarian organizations, are authorized to cultivate ganja for religious purposes as a sacrament in adherence to the Rastafarian faith.
25. Ganja that is cultivated under such authorization may not be smoked in public places other than at locations registered as places of Rastafarian worship or events with special exemption.

Events to celebrate/observe the Rastafarian faith

26. Events promoted or sponsored by persons who are adherents of the Rastafarian faith or Rastafarian Organizations, must be declared an exempted event.
27. Where an event is declared exempt, persons who attend the event will not be liable to be arrested, detained or prosecuted for smoking ganja or possession of ganja at the event, or transporting ganja to the event, as long as they have complied with the amounts and conditions specified in the order declaring it an exempt event.

Visitors to St. Kitts and Nevis who are users of medical marijuana

28. Persons who do not ordinarily reside in St. Kitts/Nevis (tourists or visiting Nevisians who live overseas) must abide by the regulations set out.

St. Kitts Mental Health Association
P. O. Box 21 67 | Basseterre St.
Kitts I mhastkitts@gmail.com

24th July, 2018

Dr Hazel Laws
Chairperson
National Marijuana Commission
Basseterre

The St. Kitts Mental Health Association (SKMHA) has taken note that Cabinet has convened the St. Kitts & Nevis (National) Marijuana Commission tasked subsequently with the development of a final report to inform relevant policy decisions regarding marijuana (Cannabis sativa). Our professional and general membership who work with persons who use and misuse marijuana in our federation have concerns that have caused us to concentrate on the potential risks and surges in Mental, Neurological and Substance Use (MNS) Disorders associated with marijuana use. Though marijuana may be of benefit in the treatment of some conditions, before being decriminalised or legalized, the SKMHA strongly advocates that all decisions be supported by scientific evidence and be pursued in a thoroughly regulated manner that engages all stakeholders.

The following descriptions highlight our present deficits as they relate to mental health resources and the delivery of services, and the SKMHA respectfully suggests that these issues be addressed in a final report to cabinet.

1. There is still a need to enhance the mental health reform process in our federation. We suggest the completion and dissemination of the Mental Health Policy, Mental Health Treatment Protocol and Mental Health Legislation as these provide important guidelines for mental health service delivery.

2. There is a need for mental health human and infrastructure resources. In order to mitigate the effects of this potential change in legislation, mental health requires greater resources in order to cope with the increasing MNS needs of our citizens. There is a need for an increase in mental health personnel and infrastructure as well as additional psychiatrists and psychologists to enhance treatment options. Choosing additional staffing and/or funding the studies of persons interested in specialties such as addiction, child and adolescent psychiatry and psychology would be prudent. Investment in psychodiagnostic tests would also greatly enhance the mental health team's ability to provide more comprehensive psychological assessments for our people.

3. There is a need for increased mental health treatment facilities. The Psychiatric Ward of the JNF General Hospital is the only facility that provides inpatient care to persons with MNS disorders. Although improvements have been made to this facility, from time to time the admission of patients has outgrown its capacity. We are now confronted with the fact that a larger, more therapeutic and sufficiently staffed facility is required. Equally vital for our federation is the investment in organized addiction treatment services and recovery programs.

The SKMHA takes note of anecdotal and factual feedback coming from territories that have chosen to decriminalize or legalize marijuana that clearly indicate that we could anticipate what the full range of that impact would be we do not have to imagine the scenario. That possibility leaves us deeply concerned that our present reality in mental health functioning is not adequately prepared to address the adverse impact of marijuana use in some individuals.

We exercise hope that the concerns expressed here would help to inform your decision making regarding Cannabis sativa use in our federation.

Yours Respectfully,

.....

Cherrilyn Warde-Crawford
President, SKMHA