Cannabis and *Cannabis* Resin

Critical Review Preparation Document

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AmericansFor SafeAccess
Advancing Legal Medical Marijuana Therapeutics and Research

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Preface

At the "Medical *Cannabis* and Cannabinoids: Policy, Research and Medical Practice" conference that took place in Prague March 4-7, 2015, representatives from organizations of medical *Cannabis* patients from 13 countries met and established the International Medical *Cannabis* Patient Coalition (IMCPC) (now with members from 39 countries), and put together a Declaration addressing the United Nations General Assembly Special Session (UNGASS) on drugs 2016.

The Declaration called on the United Nations (UN) to take the following actions:

- Recommend that increased attention and resources be given at the national and international level to the treatment with medical *Cannabis* and cannabinoids, and its research in particular.

- Invite all countries to secure stable, safe, economically available access to medical *Cannabis* and its derivatives to everyone who is indicated medically for such treatment.

- Require that the UN General Assembly Special Session on Drugs 2016 request that Governments either:

    - exclude the *Cannabis* out of the 1961 UN Convention with no other actions, or
    - prepare, debate and accept a Special UN Convention on *Cannabis*, that would be based on the scientific evidence, human rights, and the wellbeing of societies, and
    - as suggested by the World Health Organization, re-schedules *Cannabis* to account for its medical use, and in amendment prepare special regulations for medical *Cannabis* that would not mimic those of medical opiates and opium

Introduction

Background

Current international policies on *Cannabis* are outdated and are having a detrimental impact on patients worldwide. *Cannabis* is currently classified as Schedule I and IV of the UN Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (the "Single Convention"). This scheduling was determined based on a report created by the Health Committee of the League of Nations in 1935.

The UN General Assembly must have a recommendation from the UN Commission on Narcotic Drugs (CND) to change the Scheduling of *Cannabis*. The CND makes decisions on Scheduling of substances based on recommendations from the World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD).

To date, the ECDD has not conducted an updated review on *Cannabis* despite an increasing number of countries adopting medical *Cannabis* policies. The CND in its Resolution 52/5 from 2009 requested an updated review by the ECDD and in 2013 the International Narcotics Control Board, in its annual report, invited WHO, in view of its mandate under the 1961 Convention, to evaluate "the potential medical utility of cannabis and the extent to which cannabis poses dangers to human health".

On November 16-20, 2015, the ECDD met in Geneva to discuss *Cannabis* policy as well as other substances. However, the ECDD did not produce the anticipated document. Instead, weeks after the meeting, they posted a paper by one of the ECDD members, Bertha Madras with this disclaimer: "The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization." The paper left out important requested information and was not officially reviewed by the ECDD. The ECDD did not make any other recommendation except to start collecting information for a pre-review at one of its future meetings.

Moving International Policy Forward

On April 19-21, 2016, the UNGASS will meet in New York City to discuss global drug policies. A roadmap for updating international *Cannabis* policy MUST be on the agenda. Today over two-thirds of the population of the United States (U.S.) and its territories live in regions with medical *Cannabis* laws, and over 2.5 million individuals world-wide are legally using medical *Cannabis*. Canada, Israel, Netherlands, Czech Republic, Croatia, Mexico, Chile, Uruguay, Poland, Finland, Norway, Germany, Jamaica, Australia, Italy, Columbia, and Switzerland all have national medical *Cannabis* programs and dozens of other countries are reviewing legislation.

Medical *Cannabis* programs have had a positive impact on the many individuals who are legally allowed to use *Cannabis* under the recommendation of their doctors. Furthermore, studies have shown medical *Cannabis* laws are also having positive impacts on overall public health. A 2005 study from the Journal of Acquired Immune Deficiency Syndromes found that "patients who use cannabis therapeutically are 3.3 times more likely to adhere to their antiretroviral therapy regimens than non-cannabis users." In 2014, an article from the Journal of the American Medical Association found that "States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws." A recent report from National Bureau of Economic Research stated, "Our findings suggest that providing broader access to medical marijuana may have the potential benefit of reducing abuse of highly addictive painkillers."

Administration and implementation of medical *Cannabis* distribution programs are hampered by the classification of *Cannabis* in the Single Convention. Arguably, many of the programs are in varying degrees of conflict with the treaty as well. U.S. official William Brownfield, is requesting that the UN "accept flexible interpretation" of the UN

Drug Control conventions, despite the historic role the U.S. played shaping these very treaties.

Medical *Cannabis* treatments remain unavailable in most countries around the world in part due to this UN classification. Millions of patients who suffer from medical conditions for which *Cannabis* has shown to be an effective therapy face arrest and risk of criminal prosecution because of domestic policies based on these international policies. The Single Convention Treaty has been used by governments across the globe, including the U.S., to derail or greatly restrict attempts to reform national medical *Cannabis* laws and research.

UN classification of *Cannabis*, established in 1961, failed to consider the scientific and clinical evidence of the plant's medicinal properties. Medicinal benefits of the *Cannabis* plant have been known for centuries and scientific studies conducted over the past three decades have only helped to affirm the therapeutic value. It is time for policy makers to take into account new clinical research, product safety protocols for *Cannabis* cultivation, manufacturing, and distribution, and global patient needs when forming international and domestic policies.

The Report

This document is structured according to the WHO document entitled "Guidance on the WHO review of psychoactive substances for international control." This document's structure consists of addressing 19 criteria including additional considerations on quality control, as requested by the ECDD. The criteria, reflected in the table of contents, appear in the following order: The table of contents reflects each criterion, which is numbered in a specific order as requested by the WHO document. The criteria are numbered as follows: (1) substance identification by International Nonproprietary Name (INN), chemical or other common name and trade names, other identifying characteristics, Chemical Abstracts Service (CAS) registry number; (2) chemistry, including general information on synthesis, preparation and properties; (3) ease of convertibility into controlled substances; (4) general pharmacology, including pharmacokinetics and pharmacodynamics; (5) toxicology; (6) adverse reactions in humans; (7) dependence potential; (8) abuse potential; (9) therapeutic applications, extent of therapeutic use and epidemiology of medical use; (10) listing on the WHO Model List of Essential Medicines; (11) marketing authorizations (as a medicine); (12) industrial use; (13) non-medical use, abuse and dependence; (14) nature and magnitude of public health problems related to abuse and dependence; (15) licit production, consumption and international trade; (16) illicit manufacture and traffic, and related information; (17) current international controls and their impact; (18) current and past national controls; (19) other medical and scientific matters relevant for a recommendation on the scheduling of the substance. Some sections or criteria will be grouped or discussed together, for example (6), (7), and (8) are grouped because the research conducted in abuse and dependence studies often report on adverse effects.

In the last two decades alone, medical *Cannabis* programs worldwide have begun to include robust regulations to address public health and safety issues, including diversion for non-medical use and abuse. Despite the positive impact of medical *Cannabis* laws, they are arguably in varying degrees of conflict with International treaties, in particular the Single Convention Treaty of 1961.

With the UNGASS 2016 meetings around the corner, it is time to move the process forward. Global patient populations need international medical *Cannabis* policies to evolve. It is time for the world to know about the important research surrounding *Cannabis*. The paper by Bertha Madras did not follow the structure of the WHO guidance document for reviewing psychoactive substances nor did it provide the requested information. Thus, the paper was not officially reviewed by the committee because it was deficient in a number of categories. It is our hope that this document can guide the WHO ECDD, as well as help guide the CND's recommendations to UNGASS to create a roadmap for addressing *Cannabis* policies as they relate to the Single Convention Treaty.

This report will examine the vast research on the therapeutic value of *Cannabis*, as well as accurate accounts of toxicology and related public health concerns based on research that used standardized preparations of *Cannabis*. It will explore how the endocannabinoid system and cannabinoids work to help people with Cancer, Nausea and Vomiting Induced by Chemotherapy, HIV/AIDS and Hepatitis-C, Neuropathic Pain, Hepatitis-C Virus, Chronic Pain, Multiple Sclerosis, Movement Disorders, Arthritis, Alzheimer's Disease, Epilepsy and Seizure Disorders, Glaucoma, Psychiatric Disorders, Suicide and Suicidal Ideation, Post-Traumatic Stress Disorder, Gastrointestinal Disorders as well as those who suffer from chronic or neuropathic pain. The report will end with a summary of the variety of ways *Cannabis* is controlled nationally and internationally and the policies that are needed to make safe and legal access to medical *Cannabis* available to everyone.

The following document was written using over 300 references and has been reviewed by dozens of experts and stakeholders of medical *Cannabis*. After an initial draft was completed, the document was peer-reviewed by a core review board of seven experts around the world. Their input was included into the second draft, which was created for the Americans for Safe Access (ASA) National Medical Cannabis Unity Conference 2016: A Conference on Harmonization of Global Cannabis Policy and Action held on March 18-22, 2016, in Washington, D.C. ASA is the largest medical *Cannabis* patient education and advocacy organization in the U.S. and a founding member of the International Medical Cannabis Patient Coalition (IMCPC). Participants in the conference were given the chance to peer-review the document.

Participants included patients, advocates, public health experts, lobbyists, scientists, medical and legal professionals, and other industry associates in the field of medical *Cannabis*. During the conference, a special session was also set aside for a stakeholder document review to address the comments of the participants of the conference. The stakeholder review included patient advocates, medical and industry professionals, researchers, parents, and veterans.

There is enough information in this document for weighing the decision on whether or not to move forward with a rescheduling procedure for *Cannabis* and *Cannabis* products. The report includes special attention paid to side effects, adverse events, toxicology, public health concerns, and therapeutic efficacy. The benefits of medical *Cannabis* outweigh the risk when administered under supervision of a physician and *Cannabis* products are provided with adequate quality control and standardization.

Considered by many as the standard theoretical framework from which to analyze ethical situations in medicine, the four basic principles of health care ethics are autonomy, justice, beneficence, and non-maleficence. The empirical and clinical evidence provided in this report demonstrates that by not safeguarding access to medical *Cannabis*, the basic healthcare rights of patients are restricted. When there is no legal and safe access available, patients may be forced to buy unsafe products from the unregulated illicit market. By keeping *Cannabis* illegal, medical *Cannabis* patients become criminals. This rises to the level of a public health concern when patients are unable to access safe and legal medicine.

While the evidence that *Cannabis* is medicinally useful is debated, there has yet to be a single documented case of an overdose or any evidence that a lethal dose exists for humans. However, in many areas of the world *Cannabis* is still considered unsafe while other countries consider *Cannabis* an effective and safe treatment for a variety of medical conditions.

Our understanding of the therapeutic value of *Cannabis* has changed dramatically since 1935. It is time for international medical *Cannabis* policies to be based on science and not ideology, and to reflect the experience and input of patients, clinicians, and researchers.

(1) Substance identification by International Nonproprietary Name (INN), chemical or other common name and trade names, other identifying characteristics, Chemical Abstracts Service (CAS) registry number

Cannabis (CAS registry number 8063-14-7) is a member of the *Cannabaceae* family, together with another well-known member of the family, hops (*Humulus lupulus*). The *Cannabis* plant produces compounds known as cannabinoids or phytocannabinoids, including tetrahydrocannabinol (CAS registry number 1972-08-3), cannabidiol (CAS registry number 13956-29-1), and over 100 other non-toxic structurally related compounds.

This document refers to *Cannabis* as defined by the Single Convention, Article 1, Paragraph 1(b), "Cannabis means the flowering or fruiting tops of the cannabis plant (excluding the seeds and leaves when not accompanied by the tops) from which the resin has not been extracted, by whatever name they may be designated."

(2) Chemistry, including general information on synthesis, preparation, and properties

Cannabinoids are a class or group of related compounds consisting of more than a hundred terpenophenolic compounds (currently 144 have been documented), most commonly associated with the pharmacological activity of *Cannabis*. Cannabinoids mainly exist in the *Cannabis* plant as carboxylic acids and are converted to neutral analogs by light and heat while in storage or when combusted[1]. The alkyl group at the third carbon atom is considered an important site in substrate-receptor interactions[1,2]. This group is typically a pentyl – for example, in Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabigerol (CBG), cannabidiol (CBD), and cannabinol (CBN) – but can also be a propyl, in which case the compounds are named by attaching the suffix -varin to the name of the pentylated analog, e.g., tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabigerovarin (CBGV), and cannabivarin (CBNV) – butyl (THC-C4, CBD-C4, and CBN-C4) or methyl (tetrahydrocannabiorcol, cannabidiorcol, and cannabiorcol).

Cannabis plants typically exhibit one of the three main distinctly different chemotypes based on the absolute and relative concentrations of Δ^9-THCA, CBD, and CBN (after conversion from the respective acids). Some researchers refer to these as THC or drug-type, intermediate type, and fiber-type[3,4]. Plants with more rare chemical profiles have been established, including those predominant in CBG or THCV, and those lacking any cannabinoids, for a total of five general types[5,6]. The mean content of Δ^9-THC, (including Δ9-tetrahydrocannabinolic acid [Δ^9-THCA]), in the THCA-predominant plant material has been increasing in the past few decades, due to changes in cultivation techniques and selective breeding.

The cannabinoid profile is affected most by the plant's sex, genotype, and maturity followed by environmental and other factors, such as light intensity, light cycle,

temperature, and fertilization[7,8]. Cannabinoids are produced in glandular trichomes distributed across all epidermal surfaces of the plant's aerial parts at varying degrees. The distribution of glandular trichomes and, hence, phytocannabinoids varies widely, from the lowest concentrations found in stems to increasing amounts in large leaves, subtending leaves of the inflorescences, and to the highest concentrations found in female flower bracts.

Cannabinoids are highly lipophilic, permeate cell membranes, and have the ability to cross the blood-brain barrier both when inhaled (i.e., vaporized or smoked) and ingested.

(3) Ease of convertibility into controlled substances

Currently available standardized preparations of *Cannabis* have been found to have a very low potential to be converted into controlled substances of abuse, and there is no supporting evidence of street markets existing for such psychoactive preparations[9]. Two examples of this are dronabinol and nabiximols. Dronabinol is an oral preparation of THC, isolated from the *Cannabis* plant or synthetically produced. Nabiximols are a recently licensed *Cannabis* medicine, approved and available in 27 countries, that contains equal amounts of THC and the synergistic non-intoxicating CBD. Dronabinol has also been proposed, and has demonstrated efficacy in limited trials, as a treatment for *Cannabis* use disorders[10]. There were no available peer-reviewed reports documenting a street market or conversion of medical *Cannabis* products distributed through pharmacies and dispensaries in Canada or Holland at the time this report was written.

Whole plant *Cannabis* strains that are inhaled can contain varying ratios of active constituents, and thus may vary in a range of effects, and may therefore have a higher potential for conversion into other controlled substances than dronabinol or nabiximols[11]. CBD also demonstrates a low abuse potential and has been shown to not enhance significantly the reinforcing effects of THC or positive subject effects of *Cannabis*[12].

However, no cases of diversion of these medicines have been reported[9]. This reassuring profile is consistent with clinical experience of two totemic THC-containing medicines – nabilone and dronabinol – which have been available by prescription for decades[13]. In summation, published research articles report abuse or diversion as "rare and isolated" and the street market for these psychoactive drugs was determined to be very low, if it exists[9,14].

(4) General pharmacology, including pharmacokinetics and pharmacodynamics

Humans have used drugs derived from plants since time immemorial. For millennia, the opium poppy (*Papaver somniferum)* has been utilized to lessen pain and suffering and to produce euphoria[15]. Similarly, humans have used the *Cannabis* plant (*Cannabis* spp. *Sativa, Indica,* or *Ruderalis)* for thousands of years – to reduce pain, control nausea, stimulate appetite, control anxiety, and produce feelings of euphoria[16]. While the neurochemical systems that produce the effects of opiates are separate from those

responsible for *Cannabis*' activity, both of these naturally occurring materials rely on a complex internal system of receptors and biochemical messengers to exert their effects on our brain and bodies. The science of a distinct "endocannabinoid" system is a relatively new discovery, which continues to reveal a remarkable number of comparatively safe therapeutic potentialities.

The first cannabinoid, cannabinol, was isolated in 1899 and its structure elucidated in 1940, but it was not until 1964 that THC (the (-)-*trans*-Δ^9-THC isomer), the psychotomimetically active (primary euphoriant) substance in *Cannabis*, was isolated, and its structure and absolute configuration determined[17-21]. The cannabinoid compounds are derived from real cannabinoid compounds in the plant, cannabinoid acids. The first one, cannabidiolic acid, was isolated and identified by Krejčí and Šantavý in 1955 [20,22,23]. Since the discovery of THC, researchers have made some compelling discoveries. These discoveries help us to better understand how and why *Cannabis* and cannabinoid-based medicines have proven to work so well, for so many diverse maladies[24]. The evidence that these substances have the potential to be medicinally useful is overwhelming[25-28].

The therapeutic benefits of the *Cannabis* plant is derived from the interactions of its constituent cannabinoid molecules with the human body's own endocannabinoid system (ECS). The receptors of the ECS were discovered by Dr. William Devane in 1988[29]. After this discovery, Dr. Lumír Hanuš isolated endocannabinoids from mammalian brains[30-35].

The ECS modulates multiple and complex signaling pathways – a system responsible for regulating a variety of key physiological processes including movement, mood, memory, appetite, and pain[31].

One of the world's leading cannabinoid researchers, Dr. Ethan Russo, offers this comprehensive description of the ECS and its importance to a variety of physiological functions:

"*The analgesic and palliative effects of the cannabis and cannabinoid preparations have been amply reported over the past generation....*" *In essence, the effects result from a combination of receptor and non-receptor mediated mechanisms. THC and other cannabinoids exert many actions through cannabinoid receptors, G-protein coupled membrane receptors that are extremely densely represented in central, spinal, and peripheral nociceptive pathways. Endogenous cannabinoids (endocannabinoids) even regulate integrative pain structures such as the periaqueductal gray matter. The endocannabinoid system also interacts in numerous ways with the endogenous opioid and vanilloid systems that can modulate analgesia, and with a myriad of other neurotransmitter systems such as the serotonergic, dopaminergic, glutamatergic, etc., pertinent to pain. Research has shown that the addition of cannabinoid agonists to opiates enhances analgesic efficacy markedly in experimental animals, helps diminish the likelihood of the development of opiate tolerance, and prevents opiate withdrawal.*

Researchers have suggested that a clinical endocannabinoid deficiency may underlie the pathogenesis of migraine, fibromyalgia, idiopathic bowel syndrome, and numerous other painful conditions that defy modern pathophysiological explanation and lack adequate treatment.[36]"

More than 20 years since researchers began developing an understanding of the ECS, two types of cannabinoid receptors – CB1 and CB2 – have been identified, setting the stage for discoveries that have dramatically increased our understanding of how *Cannabis* and its many constituent cannabinoids affect the human body[37,38]. CB1 receptors are found predominantly in the central nervous system, particularly in the brain, and in organs and tissues such as the eyes, lungs, kidneys, liver, and digestive tract[13]. The brain's receptors for cannabinoids far outnumber the presence of all other neurotransmitter receptors combined. The relative safety of *Cannabis* is, at least in part, explained by the fact that these otherwise numerous cannabinoid receptors are virtually absent from those regions of the brainstem responsible for vital functions such as breathing and heart control. In comparison, CB2 receptors are primarily located in tissues associated with immune function, including the spleen, thymus, tonsils, bone marrow, and white blood cells[13]. The ECS consists of more than just CB1 and CB2 *Cannabis* compounds such as CBD also interact with serotonin (i.e., $5HT_{1A}$) and adenosine (i.e., A_2A) receptors[39-45]. There are a number of orphan receptors that are recognized as novel therapeutic targets that also appear to play a role in *Cannabis* pharmacology[46-50].

Ongoing research is helping scientists and physicians to increasingly understand the crucial role of the ECS in regulating a variety of key bodily functions. As best noted by the researcher who first isolated and identified THC – Dr. Raphael Mechoulam – the discovery of the ECS has generated a great deal of interest in identifying opportunities for the development of a wide variety of *Cannabis*-based and synthetic cannabinoidergic therapeutic drugs[51-53].

(5) Toxicology

The field of toxicology and related areas of study exist to define and codify the toxic effects exerted by administered drugs on the body and mind. The toxicology associated with *Cannabis* administration in humans has been extensively measured, via numerous pre-clinical and clinical studies. Using batteries of standardized tests, each study sought to compare brain health, function, and/or cognition of an individual affected with *Cannabis* to that of a "normally" functioning individual[54-57].

There has been a historical and intensive effort to address those public health concerns related to the use of *Cannabis* and its effects on cognition[5]. Negative effects on cognition or brain health (i.e., "toxic" effects) are most often defined as any statistically significant deviation from a "normal" mean[58-62]. This mean is calculated by quantifying a battery of neuropsychological tests (i.e., memory, emotional cueing, and coordination tests) and brain imaging techniques (e.g. computed tomography [CT] or magnetic resonance

imaging [MRI]). Whereas the former is useful for assessing aberrant behavioral, motoric, and learning effects, imaging is most useful in determining any abnormalities in physical brain structure and/or function caused by the intake of a drug.

Since concerns of *Cannabis* toxicity were first raised over perceived negative effects of *Cannabis* on brain health, unbiased investigation has remained somewhat problematic due to restrictions and objectives of traditional funding sources as they relate to *Cannabis* research[63-66]. When negative ideological rhetoric guides health policy, rather than empirical scientific findings, reports of outcomes are often exaggerated or distorted prior to public presentation[4,63,66-68]. Further, the results of extensive animal research may not appropriately represent the complex realities found in human populations, and thus proper human studies must be adequately controlled and conducted to define actual toxicology[69].

Hence, the focus of this report is derived from evidence generated by controlled human studies, with a preference towards investigations of standardized preparations of *Cannabis* of known purity, provenance, content, and pharmacokinetic profile, over studies that are not properly controlled for variables or that do not include any dose-response, neuroimaging, neurochemical, or anatomical correlates.

An overview of existing research on the subject of potential harm to human brain health from the effects of *Cannabis* is provided below.

Evidence Regarding Toxic and Lethal Dosing of Cannabis Preparations

A lethal toxic overdose of *Cannabis* or its preparations has never been documented, nor has there ever been evidence that an attainable lethal dose of plant cannabinoids exists for humans. In basic research, human primary brain cells, cultured *in vitro*, exposed to excessively high amounts of THC – the primary active compound found in *Cannabis* –- do not suffer any measurable toxic effects such as apoptosis or necrosis[70].

Drugs used in medicine are routinely given what is called an LD_{50}[71]. The LD_{50} rating indicates at what dosage 50% of test subjects receiving a drug will die as a result of drug-induced toxicity. Whereas toxicological investigations are meant to evidence the LD_{50} of a drug, currently there is no known LD_{50} either for *Cannabis* or for any of its major components in humans. While a number of studies have *attempted* to determine an appropriate LD_{50} rating for *Cannabis* in test animals, researchers have continuously been unable to give animals enough natural *Cannabis* to induce a death.

At present, it is estimated that the *human* toxicity of *Cannabis* is around 1:20,000 or 1:40,000. In layman terms, this means that in order to induce death, a *Cannabis* smoker would have to consume 20,000 to 40,000 times as much *Cannabis* as is contained in one *Cannabis* cigarette[72-74].

According to the U.S. Drug Enforcement Administration (DEA) hearing testimonials, the accepted theoretical calculations for an LD_{50} of *Cannabis* were originally derived from a 1969 article by Todd Mikuriya, MD, which originated from a two-page 1968 position paper (without attributed authors) in the *Journal of the American Medical Association*[75,76]. In his paper, Mikuriya also estimated the lethal doses for *Cannabis* based on references to two previous papers by Loewe[77,78]. Neither prior to, nor since, has there been any real-life evidence of a human *Cannabis* toxicity-induced death to validate Mikuriya's estimated LD_{50}.

A U.S. National Institute on Drug Abuse (NIDA)-supplied *Cannabis* cigarette weighs approximately 0.9 g. Therefore, a person would have to consume nearly 1,500 *pounds* of *Cannabis* within a 15-minute period to induce a theoretically lethal response. Unlike opiates, *Cannabis* compounds, such as THC, do not depress respiration and cannot depress respiratory drive due to sparse receptor density in medullary respiratory centers of the human brain[79,80]. In practical toxicological terms, *Cannabis* alone simply cannot induce a lethal outcome as a result of drug-related toxicity.

Summary of basic toxicology: Based on current understanding of basic toxicity research – sedation, cytotoxicity, genotoxicity, etc. – *Cannabis* and its components seem to have a uniquely wide safety margin[81-84]. To date, there has never been a single well-documented case of human fatality attributable to an overdose of *Cannabis* or its components, and no experimental or non-extrapolated LD_{50} can be attributed to a toxic or lethal overdose of *Cannabis* or a preparation thereof.

Clinical Toxicological Studies of Cannabis and Brain Function: IQ and Psychological Tests

Numerous assessments of brain function and IQ have been carried out in cohorts or groups studied from nearly every part of the world. The available evidence on effects of *Cannabis* on the brain come from wide-ranging human studies in the Caribbean, Latin America, North America, the Mediterranean, South Asia (Australia, New Zealand) and Europe. Most studies find a significant difference in brain function related to current *Cannabis* use (i.e., the day of the test), but show no consistent, reproducible, or significant long-term effects when study participants remain abstinent[85]. Results of long-term *Cannabis* use on brain health are often confusing and not statistically significant. As one clinical researcher noted in a review, "current human observations on the effects of marijuana [*Cannabis*] on development are sparse and contradictory[86]".

A review and summary of the existing human clinical evidence is provided below:

Clinicians in Jamaica administered a series of 19 neuropsychological tests to both chronic *Cannabis* users and naïve controls with no major differences between groups, except that the *Cannabis* users scored significantly higher on the Wechsler Adult Intelligence Scale (WAIS) Digit Span performance ($p<0.05$)[87]. The authors concluded that "there is no

evidence that long-term use of *Cannabis* is related to chronic impairment[87]".

A study of [*Cannabis*] hashish users and naïve controls, matched for age and socio-economic status, noted no differences in total on Performance IQ (PIQ) scores on the WAIS, but the controls performed somewhat better on three subtests involving Comprehension, Similarities, and Digit Symbol Substitution[88]. However, with less than a 7 PIQ difference, normally found in Greece population studies, the authors were led to conclude that "these observations do not provide evidence of deterioration of mental abilities in hashish users[87]."

An extensive battery of neuropsychological tests showed no *Cannabis*-induced pathological changes in a Costa Rican population study. The authors stated, "we failed to uncover significant differences between user and nonuser groups – even in those subjects who had consumed *Cannabis* for over 18 years[89]". When a follow-up study was performed on some of the members of this long-using cohort, initially there were significant differences claimed, but a subsequent critical analysis of the results reported that the effects were reduced below a meaningful statistical significance[90,91].

Another study investigated the effects of *Cannabis* on "cognitive decline" in 1,318 adults under the age of 65, over a period of 12 years. Using the Mini-Mental State Examination (MMSE), the study evidenced no significant differences in the degree of decline amongst heavy, light, and *non*-users of *Cannabis*[54,92].

The book *Cannabis and Cognitive Functioning* is a series of summarized studies in which the author studied subjects using *Cannabis* at least twice a week, on average, for a period of 3 years[93]. The author stated (p. 227), "the weight of the evidence suggests that the long-term use of *Cannabis* does not result in any severe or grossly debilitating impairment of cognitive function." The author did note more subtle difficulties in attention parameters, including an increased predilection for subtle distraction, loose associations, and likelihood of intrusion errors during memory tasks. In another review of cognitive effects of *Cannabis* by the same author, it was observed that "the long term risks for most users are not severe and their effects are relatively subtle…[94]"

A North American study on individuals aged 30-55 years old divided participants into 3 groups: 1) current daily users who had smoked *Cannabis* at least 5,000 times, 2) former users who had smoked *Cannabis* at least 5,000 times but had used *Cannabis* no more than 12 times in the prior 3 months, and 3) non-users, who had not consumed *Cannabis* more than 50 times in their lives[85]. Subjects underwent a 28-day washout period with tests performed at 0, 1, 7, and 28 days of abstinence. This study found that "users showed virtually no significant differences from control subjects on a battery of 10 neuropsychological tests[85]." The authors also concluded that former heavy users who had not consumed *Cannabis* in the last 3 months "showed no significant differences from control subjects on any tests during testing days." This study suggests that any induced cognitive deficits attributable to *Cannabis* use exist as reversible phenomena, associated

with recent *Cannabis* exposure and not due to any irreversible toxicity.

A New Zealand birth cohort study, involving 1,037 participants, found an average drop in IQ of 8 points (within a somewhat higher degree of variability; +/- 14 IQ points) at age 38 in *Cannabis* users that had used at least 4 days per week, versus non-users[95]. The authors stated, "a limitation is that we obtained information on past-year *Cannabis* dependence and self-reported frequency of *Cannabis* use with no external validation of use (e.g., biological assays)[95]."

Another New Zealand study of 111 participants found that "current users of *Cannabis* containing CBD (a second and non-psychoactive cannabinoid found in natural *Cannabis*), as well as former users, showed no structural or neurochemical hippocampal differences compared with controls[96]." The experimental cohort that was exposed to THC and no reported CBD demonstrated temporary changes in hippocampal volumes, but these effects were not significant if the users reported using *Cannabis* containing CBD. The authors stated "users exposed to CBD and former users did not differ from controls on any measure[96]."

Most recent findings suggest that low to moderate adolescent *Cannabis* use is associated neither with IQ nor with lower educational performance once adjustment is made for potential confounding data – in particular, adolescent cigarette use[57]. A sample of 2,235 teenagers participated in a United Kingdom (UK) study, which adjusted for pre-exposure to *Cannabis*, cigarette use, alcohol use, childhood mental-health symptoms, and behavioral problems. *Cannabis* use itself was not found to be causally related to lower IQ or poorer educational performance. The authors concluded that "modest *Cannabis* use in teenagers may have less cognitive impact than epidemiological surveys of older cohorts have previously suggested[57]."

In regards to long-term cognitive effects of *Cannabis* use, a 2012 literature review of 11 peer-reviewed studies evaluating *Cannabis'* potential impact on cognitive function of over 1,000 subjects concluded, "The results of our meta-analytic study failed to reveal a substantial, systematic effect of long-term, regular *Cannabis* consumption on the neurocognitive functioning of users who were not acutely intoxicated[97]".

Summary: No scientifically significant negative neuropsychological sequelae have yet been attributable to *Cannabis* usage. Arguably, some of these studies remain limited by a number of factors that need to be controlled in future investigations. Primarily, *Cannabis* use and dosing needs to be confirmed in users with biological and chemical tests, as issues of dosing and patterns of use are confounding factors when not adjusted for. "The results of our meta-analytic study fail[s]…to reveal a substantial, systematic effect of long-term, regular *Cannabis* consumption on the neurocognitive functioning of users who were not acutely intoxicated[97]".

Review of Toxicology of Cannabis Use in Brain Imaging Studies

Several studies have looked at small patient cohorts and have failed to find evidence of either permanent or consistent types of brain damage, abnormalities, structural brain changes, or brain tissue volume of either white or grey matter[93,98-102]. Human studies on brain structural and functional changes employing CT scans or MRIs are summarized below.

A 1977 study employed CT scans on 19 men with long durations of heavy *Cannabis* usage. Results showed no significant changes in either the ventricles or sub-arachnoid spaces[99]. The authors criticized a prior study for lacking controls on antecedent head trauma or other causes of neurological damage[100]. In the same issue of the *Journal of the American Medical Association*, an additional study on another cohort of 12 heavy *Cannabis* smokers displayed no CT abnormalities[101].

In 1983, brain CT scans were studied from 12 subjects who smoked more than 1 g of *Cannabis* daily for 10 years. Out of the 12 subjects, only 1 subject with a concomitant history of alcoholism showed any abnormalities compared to controls[102,103].

In 2000, no abnormalities were ascertained in a study that employed automated imaging analysis with MRI to examine 18 young/heavy *Cannabis* users. The authors stated "frequent marijuana use does not produce clinically apparent MRI abnormalities or detectable global or regional changes in brain tissue volumes of gray or white matter, or both combined[104]." One of the leading experts in the field of *Cannabis*' cognitive effects and dependence, Dr. Nadia Solowij, stated in a 2001 publication that "there is no evidence from human studies of any structural brain damage following prolonged exposure to cannabinoids[93]."

A 2015 study based in Colorado – a U.S. state that allows *Cannabis* use for qualifying adults – examined brain morphology (via volume measurements) in a sample of 29 *adult* daily *Cannabis* users versus 29 non-users, and a sample of 50 *adolescent* daily users versus 50 non-users[105]. The researchers measured the following areas and structures of the human brain, each understood to be associated with *Cannabis* use, as follows: the grey matter, nucleus accumbens, amygdala, hippocampus, and cerebellum. The results showed no statistically significant differences between daily users and non-users, in either volume or shape, in any region of interest. The authors concluded, "the results indicate that, when carefully controlling for alcohol use, gender, age, and other variables, there is no association between marijuana use and standard volumetric or shape measurements of subcortical structures[105]."

Summary of toxicology and brain studies: Claims of brain damage and cerebral atrophy are not supported by current evidence. When controlling for pertinent variables such as age, gender, and history of alcohol use, research has not been able to show any association between the use of *Cannabis* and changes in subcortical structures[105].

(6) Adverse reactions in humans, (7) Dependence potential, and (8) Abuse potential
(These sections are grouped together as the research is inter-related, as clinical studies with humans often measure the degree of dependence and abuse potential in terms of adverse reactions.)

Cannabis dependence or *Cannabis* use disorders are an increasingly recognized problem, principally driven by Δ^9-THC[9,106]. Although standardized *Cannabis* preparations such as nabiximols, dronabinol, and flower tops (Bedrocan; Dutch Cannabis) have a very low street value and diversion is rare, all THC containing medicines share a dependence liability. However, fundamental differences exist between patients receiving licensed or regulated medicine and commercial/recreational smokers of *Cannabis* obtained in the black market[9,106]. Of clear significance are variations in active cannabinoid and other constituents, and purity. There is also a fundamental difference in the *motivations* of users; recipients of a medicine typically seek to relieve their symptoms *without* experiencing cognitive disturbance[107].

Currently available standardized preparations of *Cannabis* have been found to have a very low abuse potential. Two examples of this are dronabinol an oral preparation of THC isolated from the *Cannabis* plant, and nabiximols, a recently licensed *Cannabis* medicine, approved and available in 27 countries, that contains equal amounts of THC and the synergistic non-intoxicating CBD. Dronabinol has also been proposed, and has demonstrated efficacy in limited trials, as a treatment for *Cannabis* use disorders[10].

Cannabis strains that are inhaled can contain varying ratios of active constituents, and thus may vary in a range of effects and may therefore have a higher abuse potential than dronabinol or nabiximols[11]. CBD also demonstrates a low abuse potential and has been shown to not significantly enhance the effects of THC or positive subjective effects of *Cannabis*[12].

The incidence of intoxication and euphoria during clinical trials of nabiximols has been very low, reported by only 2.2% percent of patients[55]. Significant tolerance was not recorded during long-term dosing, and abrupt withdrawal from long-term use produced only mild and transient disturbance of sleep, mood, or appetite in a minority of subjects with no concomitant withdrawal syndrome[9].

No cases of abuse or diversions of these medicines have been reported. This reassuring profile with regard to abuse potential is consistent with clinical experience of two totemic THC-containing medicines – nabilone and dronabinol – which have been available by prescription for decades[13]. In published research articles, abuse or diversion is reported as "rare and isolated" and no evidence of street market for these drugs has been detected.

In an abuse liability study of experienced *Cannabis* smokers, higher doses of nabiximols *did* show evidence of abuse potential in comparison with placebo, but scored consistently lower on a dose-for-dose basis than dronabinol. The apparent difference in risk profile is

likely a consequence of the presence of CBD in whole *Cannabis* preparations. In brain imaging and cognitive studies, participants reporting use of *Cannabis* containing a significant content of CBD have been demonstrated not to differ from control subjects with respect to either brain volume or reported results on a battery of neuropsychological tests. The evidence to date suggests that abuse or dependence of standardized, regulated, or licensed *Cannabis* preparations is likely to occur only in a very small proportion of recipients.

Summary: Compared to nabiximols, inhaled *Cannabis* preparations have a higher abuse potential. Nabiximols also exhibits less non-serious psychological side effects as compared to oral THC preparations such as dronabinol[72,108]. Although the presence of THC in *Cannabis*-based preparations could lead to abuse or dependence, this possibility has not yet emerged with significance in clinical trials of standardized preparations of *Cannabis* administered via either the oral or oral-mucosal route. This area of investigation would benefit from further exploration in greater detail of inhaled *Cannabis* preparations.

Serious and Non-Serious Adverse Events and the Use of Medical Cannabis Preparations

Under international guidelines, a "serious adverse event" is defined as any untoward medical occurrence that requires admission to a hospital or prolongation of an existing admission, causes congenital malformation, results in persistent or significant disability or incapacity, is life threatening or results in death. A "nonserious adverse event" is defined as any untoward medical occurrence in a patient or participant; the event need not have a causal relation to the treatment. The guidelines of the International Conference on Harmonization define the 'expectedness' of an adverse event, whereby an "unexpected" adverse event is one for which "the nature or severity ... is not consistent with the applicable product information[109,110]."

A recent investigation on a cohort of 215 individuals with chronic non-cancer pain examined the safety issues of a standardized herbal *Cannabis* product (12.5% THC). The standardized *Cannabis* was dispensed to eligible subjects for a one-year period. The control group consisted of participants with chronic pain, who were not dispensed *Cannabis*. The primary outcomes measured consisted of serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Other parameters included pain and other symptoms, mood, and quality of life. The median daily *Cannabis* dose was 2.5 g/d. There was no difference in risk of serious adverse events between groups. Medical *Cannabis* users were at an increased risk of non-serious adverse events, but these were mild to moderate. There were no differences in secondary safety assessments. The authors conclude, "This study suggests that the adverse effects of medical *Cannabis* are modest and comparable quantitatively and qualitatively to prescription cannabinoids. The results suggest that *Cannabis* at average doses of 2.5g/d in current *Cannabis* users may be safe…[84]"

The next set of identified adverse events discussed and used in the subsequent text were part of an investigation that coded the adverse events to the highest standard of reporting, according to the Medical Dictionary for Regulatory Activities headings "system organ classes" and "preferred terms[111,112]." Verification of data extraction methods and use of coding according to the Medical Dictionary for Regulatory Activities were verified by a medically qualified reviewer.

Numerous reports have attributed adverse effects to *Cannabis* as an associated risk factor for psychosis and neurocognitive effects[84]. Many of these reports either focus on recreational use *without* requiring a standardized *Cannabis* product, or do not employ biological assays to confirm and assess recent *Cannabis* use in participants[83,103,113,114]. The research summary and review below consists mainly of controlled, blinded studies on adverse events concerning medical *Cannabis* preparations.

A meta-analysis of 31 studies (23 randomized controlled trials and 8 observational studies) included an analysis of *Cannabis* side effects (such as dizziness and acute anxiety)[55]. *Cannabis* medicines included in the analysis comprised of an oral-mucosal *Cannabis* spray preparation (nabiximols), oral THC (dronabinol), and oral THC-CBD. The median duration of *Cannabis*-based medicine exposure was 2 weeks (ranging from 8 hours to 12 months). The meta-analysis identified a total of 4,779 adverse events reported amongst participants assigned to the intervention.

Most of the adverse events, 4,615 (96.6%), were not serious[55]. Amongst these studies, the most commonly reported non-serious side effect was dizziness (15.5%). However, the study did find 164 *serious* adverse events. The most frequent categories of serious adverse events among medical *Cannabis* product users were respiratory (16.5%), gastrointestinal (16.5%), and nervous system disorders (15.2%), whereas nervous system disorders were the most frequently reported among the control group (30.0%). Relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]), and urinary tract infection (15 events [9.1%]) were the most commonly reported serious adverse events among people assigned to receive medical *Cannabis* preparations. There was no evidence of a higher incidence of serious adverse events following medical *Cannabis* use compared with controls among a meta-analysis of adverse events and medical *Cannabis* preparations[55].

In January of 2016, a clinical trial with a synthetic modulator (BIA 10-2474) of the endocannabinoid system was abruptly interupted[115]. This synthetic drug inhibited the activity of fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of the endocannabinoid anandamide (AEA, arachidonoyl ethanolamide), thus increasing the concentrations of AEA available to stimulate the endocannabinoid system[116]. All of the pharmaceutical companies with active programs testing FAAH inhibitors voluntarily suspended their trials after the disaster of BIA 10-2474 from the Portuguese pharmaceutical company Bial, whose phase I study in healthy subjects in France left one person brain dead and five others hospitalized[117].

FAAH is also responsible for the degradation of many other fatty acid amides in the brain and body. Inhibiting FAAH not only increases the concentration of anandamide, but also the concentrations of other fatty acid amides[118]. As the mechanism of action is entirely different from that of THC, which binds to cannabinoid receptors[43], synthetic modulators of the endocannabinoid system should be seen as entirely different to cannabinoids or *Cannabis* in terms of their potential side effects and should be judged separately.

Summary: Short-term use of existing standardized medical *Cannabis* and *Cannabis* products appear to increase the risk of non-serious adverse events. Risks associated with long-term *Cannabis* use are poorly characterized in published clinical trials and observational studies; however, the cognitive effects observed in long-term users do not appear to be permanent in nature[85]. With the exception of very limited studies on synthetic endocannabinoid system modulators, *Cannabis* medicines do not appear to cause significant serious adverse events. Three tables summarizing documented effects on controlled studies with a standardized preparation of *Cannabis* are provided below.

Table 1 Side Effects of the Cannabis Extract Sativex®

Adverse event	Acute studies		Long-term studies
	Cannabis (n = 644)	Placebo (n = 587)	*Cannabis*
Ear and labyrinth disorders			
Vertigo	4.3%	1.4%	2.3%
Eye disorders			
Blurred vision	2.2%	0.3%	1.1%
Gastrointestinal disorders			
Constipation	2.2%	0.7%	4.2%
Diarrhea	3.0%	1.5%	11.5%
Dry mouth*	7.9%	2.4%	8.3%
Nausea	10.6%	5.3%	12.8%
Oral discomfort*	2.6%	2.7%	2.9%
Oral pain*	3.3%	3.9%	7.7%
Vomiting	2.6%	1.5%	6.0%
General disorders and administration site conditions			
Application site pain*	3.3%	3.4%	5.0%
Fatigue	13.0%	7.8%	10.1%
Feeling abnormal	2.6%	0.5%	3.2%
Feeling drunk	4.5%	0.3%	4.4%
Asthenia	5.1%	2.2%	3.9%
Metabolism and nutrition disorders			
Increased appetite	2.0%	0.5%	0.9%
Nervous system disorders			
Balance disorder	2.5%	0.7%	4.2%
Disturbance in attention	4.5%	0.0%	4.4%
Dizziness	32.0%	10.2%	27.6%
Dysgeusia	4.7%	1.7%	8.0%
Lethargy	2.2%	0.9%	3.3%
Somnolence	8.9%	2.7%	8.2%
Psychatric disorders			
Disorientation	4.8%	0.9%	3.5%
Euphoric mood	2.6%	1.0%	3.8%

Source: Physician product information for the use of Sativex in the UK (GW Pharmaceuticals)

[1] Possible application site reaction.

Table 2 Adverse Events Observed in Multiple Sclerosis (MS) Patients Using Cannabis Extract (Cannador, Synthetic THC (Marinol), or Placebo

Adverse event	Short-term study (15 weeks; *n* = 611)			Long-term study (52 weeks; *n* = 502)		
	THC (Marinol; 10–25 mg)	*Cannabis extract* (Cannador) †	Placebo	THC (Marinol; 10–25 mg)	*Cannabis extract* (Cannador) †	Placebo
Dizzy or lightheadedness	59%	50%	18%	8%	10%	2%
Sleep	35%	40%	33%	8%	8%	9%
Spasms or stiffness	34%	33%	33%	14%	15%	14%
Gastrointestinal tract	30%	37%	20%	9%	12%	7%
Miscellaneous	28%	30%	22%	7%	7%	7%
Pain	26%	24%	32%	10%	17%	10%
Dry mouth	26%	20%	7%	2%	1%	1%
Weakness or reduced mobility	25%	23%	20%	10%	12%	16%
Bladder	24%	26%	23%	10%	12%	15%
Infection	15%	16%	17%	9%	11%	11%
Tremor or lack of coordination	12%	10%	8%	5%	2%	2%
Depression or anxiety	10%	9%	8%	6%	6%	5%
Numbness or paraesthesia	9%	7%	7%	5%	4%	4%
Vision	6%	8%	2%	2%	2%	0%
MS-relapse or exacerbation*	-	-	-	5%	6%	6%
Falls*	-	-	-	4%	7%	3%
Memory or concentration*	-	-	-	2%	2%	1%
Other skin problems*	-	-	-	1%	5%	6%
Pressure sores*	-	-	-	0%	1%	3%

† Cannabis extract contained 2.5 mg of Δ^9-THC equivalent, 1.25 mg of CBD, and 5% other cannabinoids per capsule.
* Not measured in the short-term study.
Source: Zajicek et al. (2003, 2005).

Table 3 Side Effects Observed in a State Clinical Trial on Oral THC and Smoked Cannabis Conducted in California in the 1980s

Adverse event	Smoked cannabis (unknown dose n=98)	Oral THC (unknown dose n=257)
Dry mouth	56.5%	44.8%
Sedation	52.1%	64.0%
Dizziness	33.1%	26.8%
Ataxia	27.1%	12.8%
Elated mood	26.6%	24.4%
Confusion	26.6%	31.6%
Anxiety	20.2%	18.8%
Depressed	18.1%	13.2%
Perceptual	15.9%	22.8%
Fantasizing	10.7%	11.6%
Orthostatic	7.5%	12.8%
Panic/Fear	7.5%	7.6%
Tachycardia	6.4%	10.0%

Source: Musty and Rossi (2001).

Toxicology, Adverse Events, and Abuse

While few significant negative health sequelae are attributable to long-term *Cannabis* usage, ongoing human use of cannabinoids as medicine will continue to elucidate the emergence of negative effects. Clinically relevant risks and public health concerns associated with long-term cannabinoid use have yet to be satisfactorily demonstrated, perhaps due to the comparatively mild withdrawal effects of THC, its primary active compound. Based on current understanding of basic toxicity research, *Cannabis* and its components seem to have a uniquely wide safety margin. Notably cannabinoids do not

depress respiratory drive, unlike opiates[79]. To date, there has never been a single documented case of human fatality attributable to an overdose of *Cannabis* or its cannabinoids. Results of meta-analytic studies have thus far failed to reveal any substantial, systematic effect of long-term, regular *Cannabis* consumption that is not reversed by abstinence.

Pulmonary issues associated with *Cannabis* smoking include chronic bronchitis, particularly chronic cough, and sputum production, with more variable effects on wheezing and generally negative effects on breathlessness. However, these issues are avoidable by using vaporizer/volatilizer technology or alternative routes of administration[119,120] . Importantly, lifetime use of *Cannabis* smoking is not associated with an increase incidence of lung cancer[121].

Another confounding factor affecting a clearer understanding of long-term, chronic *Cannabis* use is the prevalence of serious adverse events concerning untoward *Cannabis contaminants*. Lung infection from bacterial and fungal contamination of plant materials, lead and other heavy metals poisoning, bronchial irritation from foreign particulate matter such as tiny pieces of broken glass, concomitant use of tobacco, calamus and other cholinergic compounds[122,123]– some side effects, both serious and non-serious, are due to contaminated products found on the black market. Illicit *Cannabis* products can represent a significant public health issue, like all compounds available via the black market, and adulterants might be seen as a clear infringement of the human rights of patients to procure safe medicine. Access to *Cannabis* products manufactured under appropriate quality assurance/quality control conditions – such as those properly standardized *Cannabis* products now available in 27 countries – are associated with significantly lower prevalence of negative health issues, both serious and non-serious. The illegality of *Cannabis* is a threat to the safety of using *Cannabis* as a medicine. Programs for supporting qualified individuals to access *Cannabis*, global product safety guidelines, or licensed/regulated *Cannabis* testing facilities help to ensure that the rights of medical consumers are respected.

How Safe is Cannabis?

Research continues to demonstrate that *Cannabis* and its preparations have an excellent safety profile. According to the Drug Awareness Warning Network Annual Report, published by the Substance Abuse and Mental Health Services Administration (SAMHSA), which contains a statistical compilation of all drug deaths that occur in the U.S., not a single death has ever been recorded due to the use of *Cannabis*.

DEA Chief Administrative Law Judge, Francis Young, in response to a petition to reschedule *Cannabis* under federal law concluded in 1988 that, "*In strict medical terms marijuana is far safer than many foods we commonly consume.... Marijuana in its natural form is one of the safest therapeutically active substances known to man. By any measure of rational analysis marijuana can be safely used within the supervised routine*

of medical care[73]*".*

(9) Therapeutic applications, extent of therapeutic use and epidemiology of medical use

Developing Protocols for Medical Cannabis

Physicians and health care providers have recently begun to develop clear protocols for treating patients with *Cannabis*-based medicines. For example, the University of California Center for Medicinal Cannabis Research (CMCR) in the U.S., completed a series of randomized clinical trials with patients and has published their guidelines for medical care[124]. These guidelines suggest that *Cannabis* therapeutics, like any other treatment mode, should be based on careful assessment of the patient's condition with consideration for other possible treatments. A possible treatment decision-tree for physicians, similar to those guidelines established by the Medical Board of California for doctors (using neuropathic pain as an example), is described below:

Physicians recommending medical *Cannabis* should:

1. Take a history and conduct a good faith examination of the patient.
2. Develop a treatment plan with objectives.
3. Provide informed consent, including discussion of side effects.
4. Periodically review the treatment's efficacy.
5. Obtain consultations, as necessary.
6. Keep proper records supporting the decision to recommend the use of medical *Cannabis*.

The Therapeutic Potential of Cannabis

Whereas research in the U.S. has been historically restricted by a prevailing Federal prohibition on *Cannabis* and cannabinoids in the past, recent global discoveries have driven interest amongst scientists to investigate the now more than 100 different cannabinoids thus far identified in the *Cannabis* plant. Entire organizations have emerged, dedicated to basic medical and clinical research on the cannabinoid molecules. The International Cannabinoid Research Society (ICRS), formally incorporated as a scientific research organization in 1991, holds an annual international research symposia, and since its inception, the membership has more than quadrupled (www.icrs.co). The International Association for Cannabinoids as Medicine (IACM), founded in 2000, publishes a bi-weekly newsletter and holds a biennial symposium to highlight emerging clinical research concerning *Cannabis* therapeutics (www.cannabis-med.org). The University of California established the Center for Medical Cannabis Research (CMCR) in 2001 to conduct scientific studies to ascertain the general medical safety and efficacy of *Cannabis* products. In 2010, the CMCR issued a report on the 14 clinical studies it has conducted, most of which were U.S. Food and Drug Administration (FDA)-approved, double-blind, placebo-controlled clinical studies that demonstrated that *Cannabis* can control pain – in some cases better than all available alternatives[124]. More recently, the

International Cannabis and Cannabinoid Institute (ICCI) was founded in the Czech Republic[125]. The goal of ICCI will be to identify, coordinate, and support global research priorities for the advancement of *Cannabis* and cannabinoid treatments through a multidisciplinary evidence-based approach that incorporates innovative tools and approaches (www.icci.science). Each of these international research organizations is dedicated, at least in part, to properly controlled, methodological scientific exploration into the therapeutic potential of *Cannabis* and the cannabinoids.

Emerging Clinical Data

To date, more than 30,000 modern peer-reviewed scientific articles on the chemistry and pharmacology of *Cannabis* and the cannabinoids have been published, and more than 1,500 articles investigating the body's natural endocannabinoids are published every year. In recent years, modern gold-standard placebo-controlled human trials have also been conducted.

A 2009 review of clinical studies conducted over a 38-year period found that "nearly all of the 33 published controlled clinical trials conducted in the U.S. have shown significant and measurable benefits in subjects receiving the treatment[37]." The review's authors made particular effort to note that cannabinoids have the capacity for analgesia through neuromodulation in ascending *and* descending pain pathways, neuroprotection, and by anti-inflammatory mechanisms – all of which indicate that the cannabinoids found in *Cannabis* have applications in significantly managing chronic pain, muscle spasticity, cachexia, and other variously debilitating conditions.

Currently, *Cannabis* is most often recommended as a complementary or adjunctive medicine. However, there exists a substantial consensus amongst experts in the relevant disciplines – including the American College of Physicians – that *Cannabis* and cannabinoid-based medicines have undeniable therapeutic properties that could potentially treat a variety of serious and chronic illnesses. What follows is a brief, annotated compilation of the emerging clinical data in support of the therapeutic usefulness of the cannabinoids.

Cancer

Cancer patients undergoing radiation and/or chemotherapy often suffer from significant nausea, pain, and other unpleasant side effects of their treatment. The effects of oral THC and mixed cannabinoid administration has been studied in more than 35 clinical trials for the treatment of chemotherapy-induced nausea and vomiting, and more than 40 clinical studies have looked at appetite modulation by cannabinoids. Years before any U.S. State authorized the medical use of *Cannabis*, a 1991 Harvard Medical School study revealed that nearly *half* (44%) of U.S. oncologists were recommending *Cannabis* to their patients as a way of mitigating side effects associated with cancer treatment[126].

In its 1999 review, the Institute of Medicine (IOM) concluded that *Cannabis* could be a valid, safe medicinal alternative for many people living with cancer[127]. Specifically, the IOM notes state, "In patients already experiencing severe nausea or vomiting, pills are generally ineffective, because of the difficulty in swallowing or keeping a pill down, and slow onset of the drug effect[128]." Cannabinoid medicines are both safely, and somewhat easily, formulated into both inhalable and suppository formats.

Since the release of the IOM report, new research has been published which clearly supports the use of *Cannabis* and the cannabinoids to curb the debilitating effects of cancer treatments. In 2001, a review of clinical studies of individuals with cancer, conducted in several U.S. states spanning multiple decades, revealed that inhaled cannabinoids and oral cannabinoids (in 591 and 1,281 subjects, respectively) were significantly effective anti-emetics versus the nausea and vomiting of chemotherapy[129]. Other studies have come to similar conclusions – that the active components in *Cannabis* produce palliative effects in cancer patients by preventing nausea, vomiting, and pain while stimulating appetite.

Beyond these palliative effects, the tumor-fighting properties of the cannabinoids have also been demonstrated in numerous pre-clinical studies, withstanding a successful Phase I clinical study looking at the safety of THC in patients with recurrent brain cancer. Researchers have observed that "these compounds [are] shown to inhibit the growth of tumor cells in culture and animal models by modulating key cell-signaling pathways. Cannabinoids are usually well tolerated, and do not produce the generalized toxic effects of conventional chemotherapies[130]."

Combating Nausea and Vomiting Induced by Chemotherapy

Cannabis is used most often to combat the nausea and vomiting induced by chemotherapeutic agents, as well as pain caused by various cancers. More than 35 human clinical trials have sought to examine the effects of phytocannabinoids or synthetic cannabinoids on nausea, including several U.S. state-sponsored trials that took place between 1978 and 1986[126,131]. In reviewing this literature, scientists have concluded that, "THC is superior to placebo, and equivalent in effectiveness to other widely-used anti-emetic drugs, in its capacity to reduce the nausea and vomiting caused by some chemotherapy regimens in some cancer patients[131]."

A 1998 review by the British House of Lords Science & Technology Select Committee concluded, "cannabinoids are undoubtedly effective as antiemetic agents in vomiting induced by anti-cancer drugs. Some users of both find *Cannabis* itself more effective[132]." The House of Lords review was built upon data provided in a 1997 inquiry by the British Medical Association that further determined that natural *Cannabis* is, in some cases, more effective than synthetic THC (i.e. dronabinol)[133].

Previous clinical work has shown that orally administered synthetic cannabinoids

(nabilone and dronabinol) are superior to dopamine receptor antagonists in preventing chemotherapy-induced nausea and vomiting. Until recently, there was not adequate information available on the tolerability of an acute dose titration of a standardized whole-plant *Cannabis* medicine; the results of clinical work suggest that rapid titration of a standardized *Cannabis* medicine appears to be well tolerated by most patients and efficacious in reducing the incidence of delayed nausea and vomiting[134,135].

Antineoplastic Actions of Cannabinoids

Recent scientific advances in the study of the endocannabinoid system have yielded exciting new leads for potentially groundbreaking anti-cancer treatments. In the past decade, preclinical studies, conducted both *in vivo* and *in vitro*, have demonstrated that different cannabinoids might have a remarkable effect in fighting different types of cancer cells. To date, studies have shown that cannabinoids arrest many kinds of cancer growths, both through the promotion of apoptosis (a.k.a. programmed cell death) and by arresting angiogenesis (blocking increased blood vessel production). Cannabinoids have also been shown to halt the proliferation, or spread, of cancer cells in a wide variety of cancer types. Unlike conventional chemotherapy treatments – that work by creating a toxic environment in the body, and are frequently responsible for compromising overall health – cannabinoids have been shown to selectively target tumor cells, leaving healthy surrounding cells undisturbed.

Cannabinoids and Tumor Reduction

The direct anti-tumor and anti-proliferation activity of cannabinoids, specifically CB1 and CB2 agonists, have been demonstrated in dozens of studies across a range of cancer types, including brain (gliomas), breast, liver, leukemic, melanoma, pheochromocytoma, cervical, pituitary, prostate, and bowel[130,136-154]. Evidenced anti-tumor activity has led to regression of tumors, reductions in both vascularization (blood supply) and metastases (secondary tumors), as well as the direct destruction of cancer cells (apoptosis) in laboratory animals and *in vitro* human tissues[155-158]. A 2009 review of recent studies on the role of cannabinoids and cannabinoid receptors in the treatment of breast cancer notes that research on the complex interactions of endogenous cannabinoids and receptors is leading to greater scientific understanding of the basic mechanisms by which *all* cancers develop[137,156].

Cannabinoids have been shown to inhibit tumor growth in laboratory animals in multiple studies [137,159,160]. In one study, injections of synthetic THC eradicated malignant brain tumors in one-third of treated rats, and prolonged lifespan in another third by as long as six weeks. Other research on pituitary cancers suggests that cannabinoids may be the key to regulating human pituitary hormone secretion [161,162].

Research published in 2009 found that the non-intoxicating cannabinoid, CBD, inhibits the invasion of both human cervical cancer and human lung cancer cells. By

manipulating CBD's up-regulation of a tissue inhibitor, researchers may have revealed the mechanism behind CBD's tumor-fighting effects[163]. A further *in vivo* study demonstrated "a significant inhibition" of lung cancer metastasis in mice treated with CBD[164]. The mechanism of the anti-cancer activity of CBD and other cannabinoids has been repeatedly demonstrated in both breast and brain cancers[165-168].

The anti-tumor effects of the cannabinoid THC on cholangiocarcinoma cells, an often-fatal type of cancer that attacks the liver's bile ducts, has also been evidenced. A 2009 study found that "THC inhibited cell proliferation, migration and invasion, and induced cell apoptosis." Interestingly, at low concentrations, THC reduced both the migration and invasion of cancer cells, while at high concentrations, THC triggered cell-death in tumors. In short, THC both reduced the *activity* and the *number* of cancer cells[150].

Research on cannabinoids and gliomas – a type of aggressive brain cancer for which there is no known cure – holds true promise for future treatments of this devastating disease. A study that examined both animal and human glioblastoma multiforme (GBM) tumors, the most common and aggressive form of brain cancer, describes how cannabinoids minimize gliomal growth by regulating the blood vessels that supply the tumors[169]. In another study, researchers demonstrated that the administration of CBD significantly inhibits the growth of subcutaneously-implanted 87 human glioma cells in mice[163]. The authors of the study noted that CBD *alone* was capable of producing a significant antitumor effect, both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as a viable antineoplastic agent in humans.

The targeted effects of cannabinoids on GBM were further demonstrated in 2005 by researchers who showed that the cannabinoid THC both selectively inhibited the proliferation of malignant cells and induced them to die off, while leaving healthy cells unaffected [70]. While CBD and THC have each been demonstrated to possess tumor-fighting properties in isolation, research published in 2010 shows that the molecules work better in combination, as CBD *enhances* the inhibitory effects of THC on GBM cell proliferation and survival [170]. More recent work in mice has confirmed this enhancing effect of CBD on THC in cancer cells in animals. The research also tested a THC/CBD combination with and without chemotherapy in the animals. The research showed that combinations of *Cannabis* compounds can significantly improve the effect of the chemotherapy agent temozolomide[160].

Similarly, researchers have demonstrated in the last few years the mechanism by which cannabinoid and cannabinoid-like receptors in brain cells regulate these cells' differentiation, functions, and viability. This is suggestive evidence that cannabinoids – and other drugs that target cannabinoid receptors – might manage neuroinflammation and thus eradicate malignant astrocytomas, a type of cancer [137,171-173]. Such recent studies confirm the positive findings of earlier studies indicating the effectiveness of cannabinoids in fighting gliomas, some of the deadliest known forms of brain cancer[136,174-176].

The potential of cannabinoids to fight cancer in humans has also been seen in three recent large-scale population studies. These studies were originally designed to find correlations between smoked *Cannabis* and cancers of the lung, throat, head, and neck. Rather, researchers discovered that the cancer rates of *Cannabis* smokers were, at worst, seen in no greater prevalence than in those that smoked nothing at all – and many fared significantly better[121]. Results of this study suggested that cannabinoids might actually have a prophylactic effect against cancer development, as seen in the anti-proliferative effect now demonstrated both *in vitro* and *in vivo*[177]. Lastly, a case report that highlights the spontaneous regression of brain cancers in two teenagers, was associated with current medical *Cannabis* use[178].

HIV/AIDS

Cannabis has proven effective in improving the quality of lives of many individuals living with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). Cannabinoid-based medicine is useful for the syndrome of HIV's effects – to help manage appetite loss, wasting, nausea, vomiting, pain, anxiety, stress, depression, and other concomitant symptoms associated with *both* the disease *and* the anti-retroviral regimen used to treat it. As many as one in four people living with HIV/AIDS use *Cannabis* for medical purposes in the U.S.[179].

An international group of nursing researchers determined from a longitudinal, multi-country, multi-site, randomized-control clinical trial that *Cannabis* is frequently used to manage the six common symptoms of HIV/AIDS. A 2009 study found that a significant percentage of those with HIV/AIDS find *Cannabis* to be efficacious for treating their anxiety, depression, fatigue, diarrhea, nausea, and peripheral neuropathies. Researchers noted that "those who did use marijuana rate it as effective as prescribed or over the counter medicines for the majority of common symptoms…[180]."

In addition to the debilitating symptoms of the disease itself, *Cannabis* has proven to be effective in controlling the unpleasant effects of the drugs used to treat HIV/AIDS. According to a 2007 study, people living with HIV/AIDS who use *Cannabis* to combat the side-effects of the Highly Active Antiretroviral Therapy (HAART therapy) are approximately *three times* more likely to remain on their prescribed drug therapies than those who do not use *Cannabis*[181].

In the 1970s, a series of human clinical trials established that *Cannabis* can stimulate food intake and thus, can cause weight gain in healthy volunteers – a finding confirmed by numerous subsequent studies. In a randomized trial in people living with AIDS, THC was seen to both significantly improve appetite and decrease nausea, in comparison to the effects of placebo administration. There were also trends towards both improved mood and weight gain. Unwanted effects – e.g. dry mouth, drowsiness and anxiety – were of generally mild or moderate intensity, and were proven to be of little consequence to the user[182-184]. The IOM's comprehensive review in *Marijuana and Medicine* concluded,

"For patients such as those with AIDS or who are undergoing chemotherapy and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication."

To address concerns involving *Cannabis*-based medicines decreasing treatment efficacy, an FDA-approved preliminary safety trial of smoked *Cannabis*, conducted in 2003 at the University of California, San Francisco, concluded that neither synthetic THC nor inhaled *Cannabis* had any significant effect on the immune system or viral load. Moreover, the researchers noted that those study participants who used *Cannabis* gained weight[184].

In addition to the overall safety demonstrated in these trials, cannabinoids may also inhibit the spread of the HIV virus within the human body by acting directly on CD4+ T cells – T cells are critical to immune function and are a target of the HIV virus. A 2012 study found that a cannabinoid activating CB2 receptors selectively produced a dose-specific reduction of HIV infection by up to 50%[185-188]. This study suggests that therapeutic use of cannabinoids might help to fight the spread of the HIV virus to uninfected T cells in the late stages of HIV-1 infection[189]. Previous research has shown that the use of cannabinoid drugs in patients with HIV is associated with an increase in CD4+ T cell number and has been shown to reduce viral load in an animal model of HIV.

Neuropathic Pain

The effectiveness of *Cannabis* and cannabinoids in managing pain has been demonstrated in more than three dozen preclinical and clinical trials, comprising more than 6,000 patient-years of data as of 2012[15]. A 2009 review noted simply: "a large number of research articles have demonstrated the efficacy of cannabinoids…[and so] cannabinoids show promise for treatment of neuropathic pain[189]."

More than one-third of people living with HIV/AIDS suffer from excruciating nerve pain in the hands or feet, frequently in response to the antiretroviral therapies that constitute first-line treatment for HIV/AIDS. This induced neuropathic pain is extremely difficult to treat and, as a result, many individuals reduce or discontinue their HIV/AIDS therapies.

A series of clinical studies of HIV/AIDS patients demonstrated that cannabinoids can significantly reduce neuropathic pain and promote weight gain, *without* compromising the immune system [190-192]. Research conducted by the University of California, San Francisco involving a randomized, placebo-controlled clinical trial of 50 people who had experienced neuropathic pain for a group average of six years, showed that smoked *Cannabis* was both well-tolerated and proved to effectively relieve chronic neuropathic pain from HIV-associated sensory neuropathies[192]. Other double-blind, placebo-controlled clinical trials with people living with HIV neuropathic pain that was not adequately controlled by other pain-relievers, including opiates, found that *Cannabis* provided significant pain relief [191]. Research also demonstrates that the use of *Cannabis*

and opiates is not associated with an increase in mortality[193].

More recent randomized clinical trials conducted by the CMCR have also demonstrated that smoked *Cannabis* is effective in treating neuropathic pain[194]. Researchers found that over half of patients with painful HIV peripheral neuropathy experienced pain reduction of more than 30% when treated with cannabinoids, a level of relief that pain researchers correlate to improved life quality. Such improvements occurred in two CMCR trials of patients with HIV peripheral neuropathies, and in a separate trial of patients with mixed neuropathic pain due to peripheral or central dysfunction of the nervous system[195-198].

Additional double-blind, placebo-controlled clinical trials indicate that *Cannabis*-based medicines may improve neuropathic pain associated with multiple sclerosis and mixed neuropathies resulting from herpes, trauma and vascular problems[15]. This research is also of particular importance to people with cancer, as many of its sufferers also experience neuropathic pain.

Finally, researchers have found that cannabinoids such as THC work *in concert* with opiate-based painkillers, to increase their combined effectiveness, particularly in cases of neuropathic pain. This evidenced synergy of *Cannabis* and opiates allowed patients to reduce their opiate dosage, minimizing the inherent risks of opiate use[199-202]. This entourage effect extends to other cannabinoids, with multiple studies finding that isolated synthetic cannabinoids such as THC (dronabinol) did not provide the same degree of efficacy as whole-plant preparations of *Cannabis*[203]. The ECS is proposed to interact with the endorphin system, both through the release of opioid peptides by cannabinoids and by the release of endocannabinoids by opioids[15,204]. Clinically, THC may enhance the pain relieving effects of opiates, effectively lowering the dose of an opiate necessary for relief[192,204]. Similarly, animal work on combined *Cannabis* and opiate administrations suggests that THC can decrease the side effects of opiates and may have a prophylactic effect on the dependence developed to opiate administration[205]. Data gathered from the U.S. in those territories that have legalized *Cannabis* for adult use, has evidenced *significantly* lower opiate-related mortality[193]. Surveys also suggest that *Cannabis* is often used to decrease the use of other drugs, most significantly opiate-based painkillers[206].

Hepatitis-C Virus

Cannabis may improve the effectiveness of drug therapy for the hepatitis C virus (HCV), a potentially deadly viral infection that affects more than 3 million Americans [207] and 130–150 million people globally. Treatment for HCV typically involves months of therapy with two powerful drugs – interferon and ribavirin – both of which have severe side effects, including extreme fatigue, nausea, muscle aches, loss of appetite, and depression. Due to the debilitating side effects of anti-HCV drug therapies, people often do not finish treatment, which worsens their symptoms and can promote irreversible harm to the liver.

Researchers from the University of California, San Francisco Medical School and the Organization to Achieve Solutions in Substance-Abuse (OASIS) found that "modest *Cannabis* use may offer symptomatic and virological benefit to some patients undergoing HCV treatment by helping them maintain adherence to the challenging medication regimen [208]." Other research has found that patients with HCV who used cannabinoids while undergoing combination ribavirin and interferon treatment were nearly *three times more likely* to complete their conventional medical treatment as compared to those participants who did not use cannabinoids.

These studies offer suggestive evidence that for patients fighting HCV, *Cannabis*-based medicine might significantly improve appetite, while offering concomitant psychological benefits such as a reduced prevalence of depression.

Chronic Pain

According to the American Academy of Pain Management, nearly 50 million Americans and more than 1.5 billion people worldwide suffer from chronic pain. Unfortunately, it is estimated that four out of every 10 people living with moderate-to-severe pain have yet to experience significant relief. After reviewing a series of trials in 1997, the U.S. Society for Neuroscience concluded that "substances similar to or derived from marijuana could benefit the more than 97 million Americans who experience some form of pain each year[136]."

Although a wide variety of prescription analgesic drugs are available for use in treating pain – from aspirin to oxycodone – *none* of these drugs can be seen as completely adequate, in light of the many, severe, and potentially deadly side-effects associated with continued opiate use.

By contrast, the safety record of *Cannabis* is remarkable, and centuries of use as an analgesic are well documented[209,210]. In their meta-analysis of the available data, the IOM acknowledged a wide historical use of *Cannabis* for pain, noting that "after nausea and vomiting, chronic pain was the condition cited most often to the IOM study team as a medicinal use for marijuana[51]." Currently, pain relief is by far the most common condition for which physicians recommend the use of cannabinoids.

Many well-designed, double-blind placebo-controlled clinical trials have demonstrated cannabinoids can reduce suffering due to neuropathic pain[135,211-215]. A broad review of the body of scientific research concerning the analgesic effects of *Cannabis* concluded that there is now unequivocal evidence that cannabinoids can be significantly anti-nociceptive (capable of blocking pain transmission) in known animal models of acute pain[204,216-219]." Further research shows that cannabinoids also produce an entourage effect that enhances the effectiveness of opiate painkillers. One animal study found that the pain-relieving dose of morphine was lowered with the addition of a simultaneous, small dose of THC. Codeine's efficiency was similarly enhanced[204]. Both human and

animal studies have demonstrated that cannabinoids can work synergistically with opioidergic drugs in relieving pain. Research suggests that both direct and indirect interactions between opioid and cannabinoid receptors can not only enhance analgesia but also reduce the development of tolerance to opiates in mammals. These interactions hold promise for developing therapeutic strategies that could provide better pain relief, with lower overall doses of opiates (oxycodone and hydrocodone), resulting in fewer dangerous, debilitating side effects that patients reliant on opiate pain-killers alone experience[219,220].

Some of the most encouraging clinical pain data involve the treatment of intractable cancer pain and hard-to-treat neuropathic pain, a type of chronic nerve pain that resists conventional treatment. Approximately 3-4.5% of the global population and somewhere between 25% and 45% of cancer patients experience neuropathic pain. Decades of research on *Cannabis'* effectiveness in pain management include several clinical human trials, with volumes of additional anecdotal evidence[189,221-226]. The prevailing scientific evidence suggests a significant efficacy of cannabinoids in treating neuropathic pain[15,135,189,212,227].

Multiple clinical trials have shown that a controlled-dosage whole-plant extract of *Cannabis* (nabiximols, GW Pharmaceuticals Ltd.) significantly relieves intractable cancer pain, and does so better than THC alone. A recent double blind, randomized, placebo-controlled trial of 360 cancer patients in 14 countries found that pain scores improved significantly with administration of *Cannabis* extract. Researchers report that the combination of natural cannabinoids in nabiximols "is an efficacious adjunctive treatment for cancer-related pain" for patients who do not get adequate relief from opiate painkillers such as oxycodone or hydrocodone[228,229].

Pain resulting from spinal cord injuries (SCI) may also be treatable with cannabinoid medicines. A research team in 2009 noted that "very few pharmacological studies have dealt specifically with neuropathic pain related to SCI," suggesting that "[for] refractory central pain, cannabinoids may be proposed on the basis of positive results in other central pain conditions (e.g. multiple sclerosis)." Animal model research of SCI pain has shown that cannabinoids yield more consistent positive results than conventional analgesics such as opiates, which "decrease in efficacy with repeated treatment over time". These investigations concluded that drugs targeting the body's cannabinoid receptors "hold promise for long-term use in alleviating chronic SCI pain[116]."

Researchers have also determined that neuropathic pain may be treatable via augmenting the body's natural supply of cannabinoids – the endocannabinoids. A study that inhibited two enzymes that normally break down the body's natural production of endocannabinoids found that preserving this efflux "reduces neuropathic pain through distinct receptor mechanisms of action" and that "[these compounds] present viable targets" for developing new analgesic drugs[230]. Drugs which can selectively target CB2 cannabinoid receptors – which are almost completely absent from the central nervous

system – have also demonstrated suggestive therapeutic potential for both inflammatory and neuropathic pain control[231].

Multiple Sclerosis

One survey of people living with multiple sclerosis (MS) showed that more than 40% of respondents report using *Cannabis* to relieve symptoms of the disease. Among them, nearly three quarters stated that cannabinoid medicines mitigated their muscle spasms, and more than half reported a significant alleviation of their pain. A similar survey found that 96% of Canadians living with MS believe *Cannabis* is therapeutically useful for treating the disease. Of those who admitted using cannabinoids to treat their symptoms of MS, the majority cited significant relief of chronic pain, spasticity, and depression[232]. In addition, numerous studies have reported improvements in tremor, sexual dysfunction, bowel and bladder dysfunction, vision dimness, dysfunctions of walking and balance (ataxia), memory loss, pain, and spasticity[233-240].

In fact, cannabinoids have been shown to significantly lessen MS symptoms, and slow or halt the progression of the neurodegenerative disease in mammals. Cannabinoid-based medicines have demonstrated effects on immune function that might serve to reduce the autoimmune neuroinflammatory response which drives relapsing neurological attacks resulting in increasing disability[241-243]. Clues as to *why* may lie in research that indicates that individuals with MS show *increased* levels of endocannabinoids in their blood, indicating perhaps that the endocannabinoid system "may be dynamically modulated depending on the subtype of the disease[244]."

Pre-clinical studies of the pharmacology of *Cannabis* have identified calmative effects on those motor systems of the CNS that have the potential to positively affect tremor and spasticity. A controlled study of the efficacy of THC in an animal model of MS – experimental allergic encephalomyelitis (EAE) – demonstrated significant amelioration of these two most common MS symptoms. A review of six randomized controlled trials of *Cannabis* extracts (that combines THC and CBD) found "a trend of reduced spasticity in treated patients" and "evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms[242]." One such dosage-controlled THC-CBD whole-plant extract – the sublingual spray, nabiximols – has been shown in numerous clinical trials to ease pain, decrease spasm frequency, and improve bladder control and quality of sleep. Clinical trials of nabiximols found "a statistically significant and clinically relevant improvement in spasticity…and was well tolerated in MS patients[245]." As of June 2012, nabiximols is available by prescription in the UK, Spain, Germany, and Denmark for the symptomatic relief of spasticity, neuropathic pain, or both, in adults with MS. It has now been approved for distribution in Italy, Sweden, Austria, and the Czech Republic, with recommendations for approval in Belgium, Finland, Iceland, Ireland, Luxembourg, the Netherlands, Norway, Poland, Portugal, and Slovakia.

MS patients frequently report that cannabinoids can help alleviate bladder control issues, and a review of studies on cannabinoid receptors in the bladder notes that non-psychoactive cannabinoids are effective, and that the psychotropic effects of THC can be mitigated by delivering cannabinoids directly into the bladder[246]. While objective measures of spasticity in humans have not consistently shown benefits from cannabinoid treatment, a randomized clinical trial with 189 MS patients being treated with a *Cannabis* extract showed that 40% achieved greater than 30% improvement[247].

In addition to studying the potential role of *Cannabis* and its derivatives in the treatment of MS-related symptoms, scientists are exploring the potential of cannabinoids to inhibit neurodegeneration. A 2003 study that the National MS Society called "interesting and potentially exciting" demonstrated that cannabinoids were able to slow the disease process in mice by offering neuroprotection against EAE [248]. Only recently have scientists identified EAE as an animal model for MS, opening the door for future investigations research into MS symptom suppression.

Other Movement Disorders

Muscular spasticity is a common condition, affecting over 12 million people worldwide. It afflicts individuals who have suffered strokes, as well as those with MS, cerebral palsy, paraplegia, quadriplegia, and a variety of spinal cord injuries. Conventional medical therapy offers little relief for spasticity. Phenobarbital (a barbiturate) and diazepam (Valium, a benzodiazepine) are commonly prescribed, but they rarely provide complete relief and many patients develop a tolerance, become addicted, or complain of heavy sedation. These drugs also often cause muscle weakness, drowsiness, and a syndrome of various untoward other side effects that patients often find intolerable.

The therapeutic use of *Cannabis* for treating muscular spasticity and movement disorders has been known to Western medicine for nearly two centuries. In 1839, Dr. William B. O'Shaughnessy noted both the plant's muscle relaxant and anti-convulsant properties, writing that medical doctors had "gained an anti-convulsive remedy of the greatest value[209]." Contemporary animal and human clinical studies reveal that *Cannabis* and its constituent cannabinoids may effectively treat movement disorders affecting older patients, including tremors and spasticity, because cannabinoids have a dose-dependent anti-spasticity, analgesic, anti-tremor, and anti-ataxic effect[233,237,249-255].

The contemporary understanding of the actions of *Cannabis* was advanced by the discovery of the endogenous cannabinoid system in the human body – the ECS – which appears to be intricately involved in regulating normal physiology[30,256,257]. Central cannabinoid receptors are densely located in the basal ganglia, the area of the brain that controls body movement. Endogenous cannabinoids also appear to play a role in the manipulation of other transmitter systems within the basal ganglia – increasing transmission of certain chemicals, inhibiting the release of others, and affecting how still others are absorbed[258-260]. Most movement disorders are caused by a dysfunction of the

biochemical loops in this part of the brain. Research suggests that an endogenous cannabinoid "tone" participates in the overall control of movement[108,261-263]. Endocannabinoids have modulating effects on the nervous system – sometimes to block neuronal excitability, while other times augmenting it. As scientists are developing a better understanding of the physiological role of endocannabinoids, it is becoming clear that these chemicals may be involved in the pathology of several neurological diseases. This means researchers are identifying an array of potential therapeutic targets within the human nervous system. They have determined that various cannabinoids found in the *Cannabis* plant modulate the synthesis, uptake, or metabolism of the endocannabinoids that underlie the progression of diseases such as Huntington's, Parkinson's, and tremors[264].

The neuroprotective qualities of *Cannabis* suggest an enormous potential for protecting the brain and central nervous system from the damaging effects of various diseases or injuries. Researchers have found that cannabinoids fight the debilitating effects of strokes, brain trauma, and spinal cord injury, as well as MS and neurodegenerative diseases. A neurodegenerative or neurological condition affects more than 52% of people over the age of 85. More than 100 research articles have been published on how cannabinoids act as neuroprotective agents, slowing the progression of a host of neurological disorders in mammals including amyotrophic lateral sclerosis, Huntington's, Alzheimer's, and Parkinson's disease[265-267].

Modern research has demonstrated some promising therapeutic effects of cannabinoids to treat Parkinson's disease and related motor neuron diseases. In one example, a female patient with Parkinsonian tremor who had failed conventional treatment claimed several hours of relief after smoking *Cannabis* on three different occasions[268]. However, when she and four other treatment-resistant patients with tremor were administered *Cannabis*, no benefit was observed on tremor in any of them in comparison to diazepam, levodopa/carbidopa or apomorphine. Two subsequent clinical trials with *Cannabis*-based medicines to treat tremor of MS, with an obviously distinct pathophysiology, produced variable benefits in some patients employing an oromucosal spray or oral extract of THC and CBD, respectively[248,269]. Data suggest that the symptom complex of Parkinsonism – including tremor, bradykinesia, and dyskinesia – may respond to such treatment over a long time course.

The best evidence for cannabinoid efficacy in Parkinson's derives from a survey performed in the Czech Republic – after a well-publicized television news magazine program presented the story of one Parkinson disease patient who improved all his symptoms with prolonged administration of an oral *Cannabis* preparation[265]. Parkinsonian patients at the Prague Movement Disorders Centre were sent an anonymous questionnaire to assess the effects of *Cannabis* on their various symptoms. Of 630 possible respondents, 339 questionnaires (53.8%) were returned. Eighty-five respondents (25.1%) reported using fresh or dried leaves taken orally approximately ½ teaspoon (2.5

ml) with meals once a day, usually in conjunction with their customary conventional medication. Almost none had prior experience of recreational *Cannabis* usage. In marked contrast to most surveys, only one respondent smoked the *Cannabis*. As a result of this oral *Cannabis* intake, 45.9% reported mild-to-substantial reduction in overall symptoms, with 30.6% noting reduced resting tremor, 44.7% alleviation of bradykinesia, 37.7% reduced muscular rigidity, and 14.1% reduction in dyskinesia associated with L-dopa medication. Noteworthy to the report was that only 4.7% felt that *Cannabis* intake exacerbated their condition.

A limited number of studies of CBD in Parkinson's disease have also been completed in Brazil[270-272]. In the first study, six Parkinson's patients with psychosis (each non-responsive for 3 months to conventional medications) were assessed in a four-week open label study. Patients were started on 150 mg CBD capsules in corn oil, with weekly increases according to clinical response[271]. Significant improvements were noted after CBD treatment in nearly *all* scored criteria, including anxiety and depression. No change was noted in motor function, nor were any cognitive changes observed.

A second study from Brazil selected 21 patients without psychiatric or dementia diagnoses from a larger cohort of 119 consecutive Parkinson's diseases evaluations [270] and employed 300 mg CBD per day in corn oil capsules vs. placebo, in a double-blinded trial for six weeks. Capsules were administered only at night. After treatment, the CBD group showed positive results in the Parkinson's Disease Questionnaire (PDQ-39) and the Activities of Daily Living and Stigma subscores.

A third Brazilian study examined a subset of Parkinson's patients with rapid eye movement (REM) sleep behavior disorder[272]. Case studies and assessments were performed on four affected patients. Three of the patients went six weeks without episodes after taking 75 mg of CBD in corn oil capsules nightly, while the fourth required dose escalation to 300 mg a night to reduce episodes to once a week. All the patients experienced relapse to attacks of the prior frequency upon discontinuation of the CBD.

An Israeli study examined 22 patients who had received government permission to try smoked *Cannabis* for treatment-resistant Parkinsonian symptoms[273]. Participants used *Cannabis* continuously for more than two months. Six proved intolerant to *Cannabis* due to inability to inhale smoke, and side effects such as vomiting, dizziness, or psychosis. Motor scores improved after *Cannabis* in patients with or without daily response fluctuations. Specifically, improvements were noted in tremor, rigidity, bradykinesia, but only slightly on posture. Pain also diminished significantly, and 20 patients reported improvement in sleep.

The available evidence to date suggests a possible application of *Cannabis*-based medicines for symptomatic treatment of Parkinson's disease. Both THC and CBD components may contribute, but exact dosing and/or appropriate ratios of these disparate

cannabinoids are still unclear using available data[274,275]. Documentation supports a benefit to inhaled and oral preparations, with the latter seemingly preferable to patients given the requirement for chronic or life-long administration. No clear drug-drug interactions have yet been noted. Overall, the data would suggest that prolonged trials of *Cannabis*-based medicines may be necessary to assess overall benefit or lack thereof.

Arthritis

According to the Arthritis Foundation, arthritis is one of the most prevalent chronic health problems and the nation's leading cause of disability amongst Americans. A 2006 report estimated that 46 million Americans – nearly 1 in 5 adults – and 350 million people worldwide, live with chronic joint pain and arthritis. Indeed, the use of cannabinoids as a treatment for musculoskeletal pain in western medicine dates back to the 1700s[276]. Modern research confirms that *Cannabis* and related therapies can relieve the pain associated with arthritis and the other rheumatic and degenerative hip, joint, and connective tissue disorders. In their 1999 meta-analysis of the data then available, the IOM specifically noted that the anti-inflammatory properties of cannabinoids could have therapeutic application in preventing or reducing pain caused by swelling and inflammation (such as arthritis)[51].

Research has proven *Cannabis* and its constituent cannabinoids possess powerful immuno-modulatory and anti-inflammatory properties that may be useful in treating chronic inflammatory diseases directly [277-280]. Many patients and doctors report *Cannabis* has proven to be an effective treatment for rheumatoid arthritis, and it is one of the recognized conditions for which many U.S. states now permit medical use.

CBD has been shown to have numerous medical applications as an anti-inflammatory and neuroprotective agent, including as a treatment for rheumatoid arthritis[281,282]. Research indicates that CBD suppresses the immune response in mice and rats that is responsible for a disease state resembling arthritis, protecting them from severe damage to their joints, and markedly improving their condition [283-285]. In a randomized, double-blind, placebo-controlled trial in 58 human patients with rheumatoid arthritis, nabiximols significantly improved pain, sleep quality, and a measure of disease activity[14].

Specifically, *Cannabis* has a demonstrated ability to improve mobility and reduce morning stiffness and inflammation, and research suggests that individuals can reduce their use of potentially harmful non-steroidal anti-inflammatory drugs (NSAIDs) when using *Cannabis* as an adjunct therapy[280,286].

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative condition for which *Cannabis* and cannabinoid therapies also show some promise, both for managing the symptoms and treating the underlying disease. Agitation is the most common behavioral management

problem in people with Alzheimer's, affecting an estimated 75% of people with the disease. It can include symptoms ranging from physical or verbal abusive behavior to pacing and restlessness, as well as disruptive behaviors such as screaming and repetitive requests for attention. Clinical research involving THC indicates that cannabinoids might significantly reduce the agitation common to Alzheimer's sufferers[287-289]. THC has also proven effective in combating anorexia or wasting syndrome, another common problem for people with Alzheimer's disease [290]. Alzheimer's disease is widely believed to be associated with oxidative stress, due at least in part, to the membrane action of β-amyloid peptide aggregates. Recent studies have indicated that the *Cannabis* plant's primary components – CBD and THC – provide a combination of neuroprotective, anti-oxidative and anti-apoptotic effects by inhibiting the release of the toxic β- amyloid peptide[291].

Epilepsy and Seizure Disorders

Peer-reviewed journal articles on the effects of *Cannabis* and related compounds from the plant have been largely limited to a concentrated series of preclinical animal studies, undertaken because *Cannabis* controls limit or prevent meaningful human clinical studies from being conducted in the U.S. There are *thousands* of published articles demonstrating the anti-convulsive and anti-epileptic effects of cannabinoid compounds in animals but that research is simply beyond the scope of this document, which focuses on human studies. In the absence of approved clinical research studies on *Cannabis* and epilepsy, the many anecdotal case reports of successful seizure control by individual patients must be assessed. Several documentaries have been filmed of parents using *Cannabis* extracts to treat childhood epilepsy. What follows are a number of compelling, though anecdotal, case reports of the benefit of a *Cannabis*-based therapy for seizures and convulsions[292].

Cannabis, THC, and Seizures

In the late 1940s, the effects of Δ^9-THC were investigated in a small trial of five institutionalized, epileptic children whose seizures had previously been unresponsive to phenobarbital or phenytoin. The study found that "*severe anticonvulsant resistant grand mal epilepsy* [was] *controlled*" in two children with no change noted in the remaining three[293].

Shortly before the 1976 drug convention lead to the U.S. adopting regulations that severely limited *Cannabis* research, another case report was published, documenting a 24-year-old male on two concurrent antiepileptic drugs, who was not able to control his seizures. Rather, the patient used 2-6 *Cannabis* cigarettes per day to control his symptoms[294]. Since the 1976 drug convention, there have been few relevant case studies available, and those that are available tend to document the efficacy and safety of THC-based therapy as an anticonvulsant treatment in terminal pediatric patients[251]. Another study documented four relevant cases of children, ages 12 to14, that were administered THC, causing a "noticeable reduction in the number of seizures" in these participants.

More recently, *Cannabis* has been reported to produce a "marked improvement" in seizure control in a 45-year-old cerebral palsy patient, epileptic since age 18, who experienced premature birth as well as a concussion at age 8[295]. While these few anecdotal stories are quite compelling, they simply do not amply delineate *Cannabis*-based medicine for seizures.

CBD and Seizures

To date, CBD is the only phytocannabinoid other than THC with reported results for anticonvulsant effects in human subjects. The following is a review of studies on CBD used to treat seizure disorders in humans. In 1978, Mechoulam and Carlini randomized nine patients to either 200 mg/day of pure CBD or placebo[296]. During the three-month trial, two of four patients treated with CBD became seizure-free, whereas seizure frequency was unchanged in the five patients who received placebo.

A small (n=15) population of adult patients who exhibited partial seizures with secondary generalization that were uncontrolled by conventional treatment were enrolled in a double-blind, placebo-controlled, add-on study to examine the effect of CBD (≤300 mg/day) for 4.5 months[292,297,298]. Of the patients who received CBD (n = 8), four exhibited no sign of seizure, one "*improved markedly*," one "*improved somewhat*," one showed no improvement, and one withdrew from the study. The investigators concluded that CBD could be of benefit to patients with secondary generalized epilepsy for whom existing medicines were ineffective.

In a later, open-label clinical trial employing CBD (900–1200 mg/day for 10 months), "*seizure frequency was markedly reduced in the patient*" consistent with previous findings[299]. In yet another study, 12 epileptic patients were given CBD (200–300 mg/day) as an adjunct to existing treatments, but no change in seizure incidence was found[300]. The results of these studies were published in only abstract form, preventing full examination of the study details and insight into the relevance of the findings.

In 2005, a study reviewed population data of epileptic children resistant to conventional anti-epileptic medications. Subsequently, the researchers instituted treatment for *some* of these subjects using an oil-based formulation of CBD. In most of the treated children, an improvement of the crises was obtained in equal to, or higher than, 25%, wherein a clear improvement of consciousness and spasticity was observed. Specific incidence of side effects was not reported in this study; however, subjects suffered no side effects warranting discontinuation of the CBD solution.

In regards to existing research on epilepsy and *Cannabis*, most of the available human evidence suggests that *both* a reduction in incidence *and* severity of seizures, as well as physical and behavioral improvements in children and adults treated with either *Cannabis* or its preparations can be achieved.

Despite the potentially beneficial effects of *Cannabis* and its constituents in the management of epilepsy, the psychotropic effects of pure THC alone limits its widespread therapeutic use, particularly as an anticonvulsant where regular, repeated doses throughout a patient's lifetime are necessary[301,302]. However, it is notable that not only are all currently approved anticonvulsant drugs associated with some significant motoric and/or cognitive side effects, but many epilepsy patients are unable to drive motor vehicles or maintain employment because of either the side effects of conventional drugs, the symptoms of the disease, or a combination of the two[292,303].

Glaucoma

Glaucoma is an eye affliction characterized by an increase in intraocular pressure. It can lead to blindness if it is not treated effectively. Several anecdotal reports observe that *Cannabis* has the power to reduce the fluid pressure within the eye (Hepler et al., 1976; Green, 1984; Grinspoon and Bakalar, 1997). The U.S. federal government sends approximately 1 pound of *Cannabis* cigarettes to each surviving glaucoma patient from a 1970's Investigational New Drug (IND) program (there are currently two surviving patients with glaucoma)[103]. Despite documented treatment success for patients in the IND program, it was cancelled for political reasons. The surviving patients were grandfathered into the program and continue to receive *Cannabis* produced by the University of Mississippi.

Despite decades of documented anecdotal reports of *Cannabis* to treat glaucoma from this IND program, only two controlled studies evaluating the effects of THC on glaucoma patients have been approved[304,305]. In a randomized, double-blind, crossover, placebo-controlled clinical trial, Merritt et al. (1980) administered one *Cannabis* cigarette containing 2% THC to 18 adults suffering from glaucoma. *Cannabis* induced a significant reduction in intraocular pressure, but exhibited the following main adverse effects: various sensory alterations (100% of the cases), tachycardia and palpitations (44% of the cases) and postural hypotension (28%).

In the other randomized, double-blind, parallel group study against placebo, conducted 1 year later, Merritt et al. (1981) instilled eye drops containing 0.01, 0.05 or 0.1% THC in eight individuals suffering from glaucoma and hypertension (one eye received THC and the other one placebo). They then observed a significant reduction in intraocular pressure with 0.05 and 0.1% topical solutions of THC. The 0.1% topical solution of THC induced a mild hypotension, but most importantly, no psychotropic effects were observed with the three locally administered THC concentrations.

Psychiatric Disorders (Anxiety, Depression, and Related Mood Disorders)

Human studies on the effects of *Cannabis* on anxiety and depression or mood disorders include studies on THC, CBD, and whole plant material. Dosing consisted of a range between 5mg-30mg oral THC and a single clinical study looked at 0.5mg/kg THC for

changes in mood and related behavior. For CBD, clinical studies examined oral doses ranging between 60mg-600mg and 1mg/kg for improvements in related mood disorders. Conversely blocking the active sites for THC with the CB1 receptor antagonist, rimonabant is capable of increasing stress and anxiety levels at an oral dose of 70mg.

Review of the Human Clinical Studies on Psychiatric Disorders

Anxiety and Mood Disorders

The effects of *Cannabis* on anxiety and depression may depend on the ratio of certain cannabinoids, the individual user, and the context in which it is used. One of the active ingredients of *Cannabis* can cause an acute and short-lasting episode of anxiety, which often resembles panic, in naïve users. For a naïve user, a dose of oral THC that is likely to start to induce anxiety is >5mg synthetic Δ^9-THC (for a man of average weight) and a higher dose could induce both panic attacks and paranoias[306]. However, the same is not necessarily true for all cannabinoids.

In a study with 10 treatment-naïve patients with generalized social anxiety disorder, 400mg oral CBD was shown to reduce anxiety compared to placebo. This anxiolytic effect was associated with significantly reduced regional cerebral blood flow (measured by uptake of 740MBq of 99mTc-ECD) in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, while increasing cerebral blood flow (ECD uptake) in the right posterior cingulate gyrus[307]. Similarly, a study of 24 patients with social anxiety disorder found an association between CBD (600mg; n=12) and decreases in anxiety within the context of public speaking task[308].

In 1974, an interactive study between CBD and THC showed that CBD (60 mg), added to Δ^9-THC (30 mg), changed the symptoms induced by THC alone in such a way that the subjects receiving the mixture showed less anxiety and more pleasurable effects [309]. In 1982, a study confirmed a similar effect with CBD (1 mg/kg), co-administered with THC (0.5 mg/kg), and this combination also significantly reduced anxiety indices in healthy volunteers [302].

An early study on *Cannabis* use in Jamaica revealed no significant differences between a group of 30 users, and matched controls with respect to mood, thought, or behavior [310]. An international study funded by the National Institute on Drug Abuse, examined a group of 47 long-term hashish users in Greece. Differences in the number of users within defined psychopathology, as compared to controls was accounted for by "personality disorders," with more psychiatric abnormalities being observed in the moderate user group as compared to heavy users [311,312]. A few years later, another study documented that *Cannabis* users in Costa Rica believed that use helped with depression. No significant adverse effects, or development of adverse health effects resulting from *Cannabis* use were observed [89].

The effects of THC are not consistent and often may misrepresent the effects of whole *Cannabis*[313]. In a study of oral THC, healthy volunteers received two doses of THC (7.5 and 15mg by mouth) or placebo, across separate sessions, before performing tasks assessing facial emotion recognition and emotional responses to pictures of emotional scenes[313]. In this three-session, double-blind, placebo-controlled study, THC significantly impaired recognition of facial fear and anger, marginally impairing recognition of sadness and happiness. The subjective responses to THC were not consistently positive – of the 25 study participants, 15 indicated a desire to take the 7.5mg dose again, whereas only 11 out of 25 did so at the higher 15 mg dose. Just over half of the participants identified THC as "marijuana-like" (7.5mg: 56%; 15mg: 52%). This study parallels many other findings on this subject – the paradox between dampened amygdalar reactivity and increased physiological indicators of emotional response remains a mystery to be resolved. The authors concluded that this property could potentially increase the appeal of *Cannabis* to certain users. As *Cannabis* use can lead to reduced sensitivity to anxiety-provoking emotional signals in some people, this may facilitate certain social interactions, especially amongst individuals with social inhibition or related disorders.

It has been well demonstrated that 'blocking' or interfering with CB1 receptor signaling can increase anxiety. One study documented that the CB1 receptor antagonist/inverse agonist, rimonabant, increases anxiety induced by public speaking in healthy humans. The anxiogenic effects occurred selectively during anticipatory and performance speech, without interfering with the pre-stress phase, meaning that the drug effects occurred selectively in response to an aversive situation [314].

Inhaled *Cannabis* and mucosal sprays – with precise amounts of key cannabinoid ingredients – do not induce the same side effects as pure THC controls[203]. Research suggests that a *Cannabis* "overdose" (i.e., anxiety, panic attack, etc.) can be treated (or prevented prophylactically) with foodstuffs such as pine nuts, lemons, basil and/or orange juice, as these foodstuffs share many relevant, pharmacologically active compounds[203].

Similar to the literature on the effects on *Cannabis* on anxiety, the effects of *Cannabis* on mood disorders are contradictory. For example, a group of authors published case reports suggesting *Cannabis* can cause an acute depressive reaction in those with underlying depression. However, their later case reports suggest *Cannabis* use can *improve* symptoms of bipolar disorders [72,312,315]. Cross sectional studies suggest that depression is associated with *Cannabis* use, and that *Cannabis* consumption is related to an increased risk of depression later in life [59,316]. Likewise for anxiety, it has been noted that "Frequent cannabis users consistently have a high prevalence of anxiety disorders and patients with anxiety disorders have relatively high rates of cannabis use [306]." It is unknown whether *Cannabis* use leads to a greater incidence of depression and anxiety later in life. In one survey, *Cannabis* use and depression were not associated once medical use was taken into account[317]. In some cases, an illness (and not the use of *Cannabis*) may be causative factor for depression. Though there is a modest increase of risk amongst problematic users of developing depression or an anxiety disorder later in life, a recent meta-analysis found that that small, but statistically significant association between *Cannabis* and

anxiety hinged on the inclusion of a single study[318]. While *Cannabis* may provide some benefit to anxiety or depressive/mood disorders in some individuals, the true relationship between *Cannabis* use and anxiety and depressive disorders later in life remains unsubstantiated by current research. Similar to anxiety, differential effects of *Cannabis* on depression may be due to differences in cannabinoid composition. Indeed, CBD has been shown to produce anti-depressant like effects similar to imipramine[319,320].

Suicide and Suicidal Ideation

Recent epidemiological work found no relation between the number of medical *Cannabis* users and completed suicides [321]. In fact, U.S. states that legalized the use of medical *Cannabis* were shown to have lower rates of suicide among men between the ages of 20 and 39, when compared to states that did not legalize medical *Cannabis* use[322].

Research among non-medical *Cannabis* using populations has received considerably more attention. Unfortunately, while some studies have shown associations between *Cannabis* use and heightened suicide ideation and attempts, a number of studies have either failed to control for confounds or, when they have, reported no association between *Cannabis* use and suicide[323-328] .

Post-Traumatic Stress Disorder

There has been a recent emergence of empirical studies on the effects of *Cannabis* for symptoms of Post-Traumatic Stress Disorder (PTSD), borne primarily out of the observation that individuals with PTSD report using *Cannabis* to cope with PTSD symptoms; specifically, hyperarousal, negative affect, and sleep disturbances[329-331]. Indeed, empirical work has consistently demonstrated that the endocannabinoid system plays a significant role in the etiology of PTSD, with greater availability of cannabinoid type 1 receptors documented among those with PTSD than in trauma-exposed or healthy controls[332,333].

Unfortunately, there have been no randomized controlled trials (RCTs) of *Cannabis* for the treatment of PTSD. However, the use of *Cannabis* and oral THC has been implicated as a potential mechanism for the mitigation of many PTSD symptoms by way of its effects on the endocannabinoid system[334,335]. Consistent with this research, there has been one small RCT of nabilone that showed promise for reducing nightmares associated with PTSD. This retrospective study identified a 75% reduction in PTSD symptoms following *Cannabis* use among combat veterans with PTSD. In an unpublished pilot study of 29 Israeli combat veterans, reductions in PTSD symptoms followed the administration of smoked *Cannabis*, with effects seen up to one year post-treatment [336,337].

Research on Cannabis and Gastrointestinal Disorders

Crohn's disease (CD) is an inflammatory bowel disease (IBD) that has no cure; treatment targets include reducing inflammation and secondary symptoms[338]. Between 16 percent and 50 percent of patients use *Cannabis* to relieve symptoms of IBD and patients using

Cannabis for 6 months or longer are five times more likely to have had surgery for their IBD[339-342]. Only one placebo-controlled study of the effects of *Cannabis* in patients with CD has been conducted[340]. This study found that there was no difference between placebo and smoked *Cannabis* on CD remission, defined as a CD Activity Index (CDAI) of less than 100, and that *Cannabis* was superior to placebo in promoting clinical response (a decrease in CDAI score greater than 100), reducing steroid use, and improving sleep and appetite[340].

Many researchers have concluded that pharmacological modulation of the endogenous cannabinoid system provides new treatment options for a number of gastrointestinal diseases, including nausea and vomiting, gastric ulcers, IBD, CD, secretory diarrhea, paralytic ileus and gastroesophageal reflux disease[343-345] .

Summary: Cannabinoids represent a provocative, mostly untapped resource for therapeutic intervention of many human diseases. The research listed here, coupled with the extensive work done on all other neuroprotective properties of various *Cannabis* components, indicates that cannabinoid-based therapies may become a primary source of effective treatments for battling the myriad central nervous system diseases that afflict hundreds of millions of people worldwide. Our growing knowledge and pharmamentarium of cannabinoidergic medicine may provide a great source of pharmacological and biochemical solace in the years to come[346,347].

(10) Listing on the WHO Model List of Essential Medicines

Cannabis, its preparations, or any derivatives thereof are not listed in the World Health Organization (WHO) Model List of Essential Medicines[348].

(11) Marketing authorizations (as a medicine)

Cannabis medicines are available in various forms in at least 30 countries[349].

(12) Industrial use

The stalk of the *Cannabis* plant has a number of industrial uses as a textile and fiber[7,350]. *Cannabis* or hemp fiber is used to make clothing, paneling, and building material, among many other uses.

(13) Non-medical use, abuse and dependence, and (14) Nature and magnitude of public health problems related to abuse and dependence

(These sections are grouped together because the research studies are inter-related and correspond).

The effects of drug or substance abuse related to public health outcomes should be considered and evaluated in comparison to other drugs and substances[351-354]. Previous analysis has shown that *Cannabis* smokers are 2.6 times more likely to have a psychotic-like experience than compared to non-smokers[355,356]. By comparison, people who smoke tobacco are 20 times more likely to get lung cancer than those who do not smoke. To put

this in perspective, over 5,000 men, 20-25 years old would need to stop using the drug in order to ostensibly prevent one episode of schizophrenia. Along with this is the paradox that while cases of schizophrenia have decreased in the last 30 years, *Cannabis* use has increased substantially amongst like populations[355,356].

Proper assessment of the harms caused by the misuse of drugs can inform policy makers when making decisions towards health, policing, and social care. The research study and figures discussed below apply a multi-criteria decision analysis (MCDA) model to demonstrate a range of drug harms. This research, based in the UK, provides the most recent comprehensive research published on comparing the harms of various drugs[357,358].

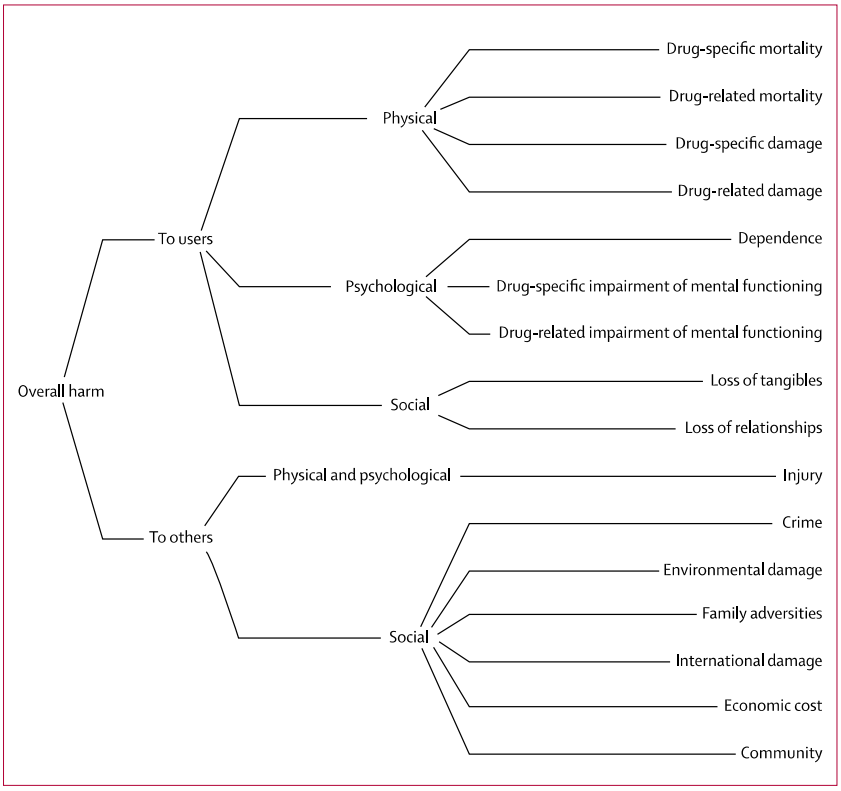

Figure 1) Evaluation criteria organized by harms to users and harms to others, and clustered under physical, psychological, and social effects. The above figure demonstrates how drug harm is measured; essentially the two major factors are harm to the drug user and harm to others.
From: Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: A multicriteria decision analysis. *The Lancet*, *376*(9752), 1558–1565.

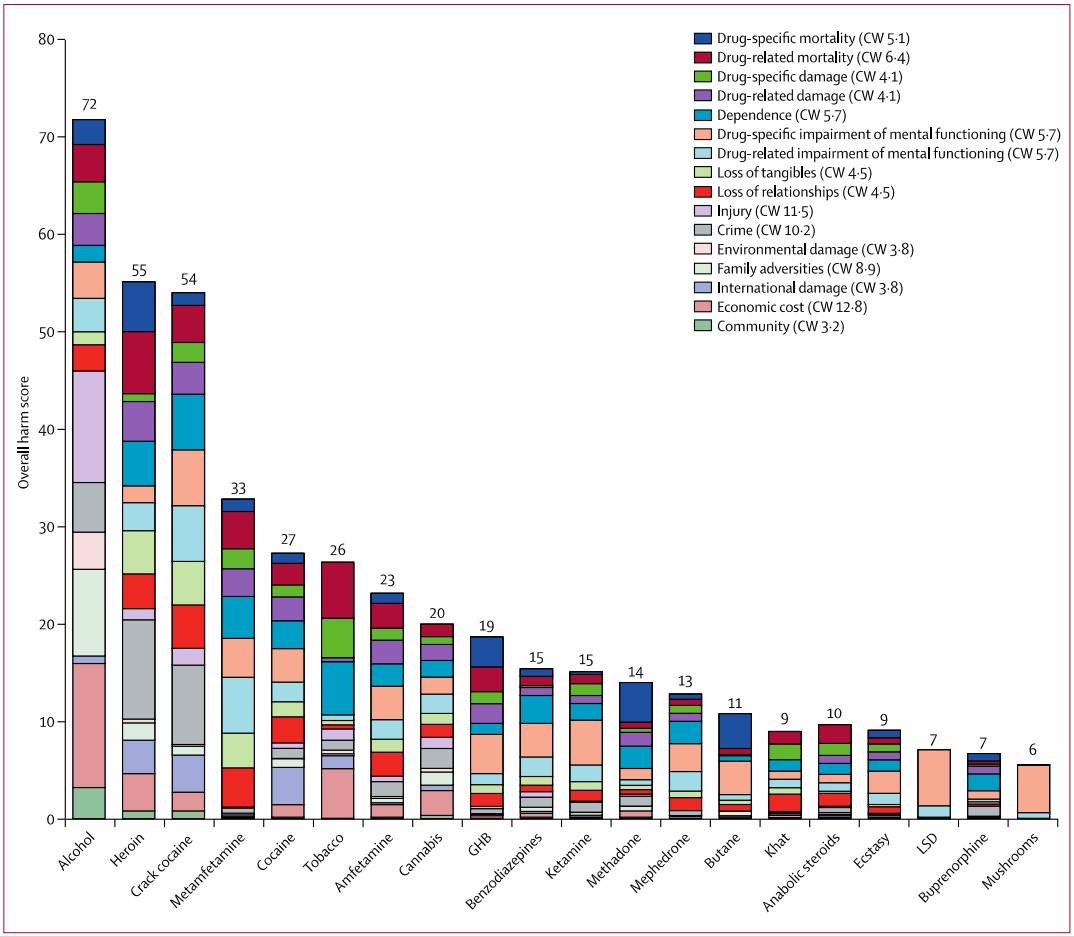

Figure 2*:* Overall weighted scores for each of the drugs
The colored bars indicate the part scores for each of the criteria. The key shows the normalized weight for each criterion. A higher weight indicates a larger difference between the most harmful drug on the criterion and no harm. CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide. The scores were generated according to the International Classification of Diseases, tenth revision of the Diagnostic and Statistical Manual of Mental Disorders, fourth revision. Nutt et al. (2010). Drug harms in the UK: a multicriteria decision analysis. *The Lancet*, *376*(9752), 1558–1565.

Definitions: **Drug-specific mortality** Intrinsic lethality of the drug expressed as ratio of lethal dose and standard dose (for adults). **Drug-related mortality** The extent to which life is shortened by the use of the drug (excludes drug-specific mortality)—eg, road traffic accidents, lung cancers, HIV, suicide **Drug-specific damage** Drug-specific damage to physical health—eg, cirrhosis, seizures, strokes, cardiomyopathy, stomach ulcers **Drug-related damage** Drug-related damage to physical health, including consequences of, for example, sexual unwanted activities and self-harm, blood-borne viruses, emphysema, and damage from cutting agents. **Dependence** The extent to which a drug creates a propensity or urge to continue to use despite adverse consequences (ICD 10 or DSM IV) **Drug-specific impairment of mental functioning** Drug-specific impairment of mental functioning—eg, amfetamine-induced psychosis, ketamine intoxication **Drug-related impairment of mental functioning** Drug-related impairment of mental functioning—eg, mood disorders secondary to drug-user's lifestyle or drug use **Loss of tangibles** Extent of loss of tangible things (eg, income, housing, job, educational achievements, criminal record, imprisonment) **Loss of relationships** Extent of loss of relationship with family and friends **Injury** Extent to which the use of a drug increases the chance of injuries to others both directly and indirectly—eg, violence (including domestic violence), traffic accident, fetal harm, drug waste, secondary transmission of blood-borne viruse. **Crime** Extent to which the use of a drug involves or leads to an increase in volume of acquisitive crime (beyond the use-of- drug act) directly or indirectly (at the population level, not the individual level). **Environmental damage** Extent to which the use and production of a drug causes environmental damage locally—eg, toxic waste from amfetamine factories, discarded needles. **Family adversities** Extent to which the use of a drug causes family adversities— eg, family breakdown, economic wellbeing, emotional wellbeing, future prospects of children, child neglect. **International damage** Extent to which the use of a drug in the UK contributes to damage internationally—eg, deforestation, destabilisation of countries, international crime, new markets. **Economic cost** Extent to which the use of a drug causes direct costs to the country (eg, health care, police, prisons, social services, customs, insurance, crime) and indirect costs (eg, loss of productivity, absenteeism). **Community** Extent to which the use of a drug creates decline in social cohesion and decline in the reputation of the community.

Members of the UK's Independent Scientific Committee on Drugs, and two invited specialists, met for a 1-day interactive workshop to score 20 drugs on harms assessment. This panel of drug-harm experts were convened to establish scores for 20 representative drugs that were relevant to the UK and which span the range of potential harms and

extent of use. The harms were assessed according to a set of 16 criteria developed by the Advisory Council on the Misuse of Drugs (the UK Government committee on drug misuse). Of the 16 criteria, nine related to the harms that a drug produces in the individual and seven were in relation to the harms of another. Drugs were scored out of 100 points, and criteria were weighted to indicate their relative importance. Overall, alcohol showed to be the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places.

Provided by Nutt et al. (2010), and created from data obtained from the workshop, Figure 2 shows a comparison amongst drugs of abuse across different scheduling and control status, with each colored bar representing a different criterion. For example, Drug-Specific Mortality, representing reported average occurrences of deaths from the substances over time, is on the top of each column. Alcohol, heroin, butane, and GHB display a notable association with higher risk of death from consumption, while *Cannabis*, anabolic steroids, khat, and LSD show very low or no association with mortality. A limiting factor of this and other data discussed here is that the substances are only scored for harm and weighted without scores or criteria regarding medical use. Another important limiting factor is that Nutt et al.'s calculations of *Cannabis* harm are somewhat overstated due to their consideration of *legal* harms in their process. Ideally, only medical factors would be the sole determinants of risk.

This is not the first study of its kind and previous research found similar results. The findings of Nutt et al. (2010) lend support to previous work in the UK, the Netherlands, the U.S. and elsewhere, confirming that the present drug classification systems have little relation to empirical evidence of harm[103,355-361]. These studies also subscribe to the conclusions of previous expert reports, that aggressively targeting alcohol harms is a valid and necessary public health strategy.

	Physical harm				Dependence				Social harm			
	Mean	Acute	Chronic	Intravenous	Mean	Pleasure	Psychological dependence	Physical dependence	Mean	Intoxication	Social harm	Health-care costs
Heroin	2·78	2·8	2·5	3·0	3·00	3·0	3·0	3·0	2·54	1·6	3·0	3·0
Cocaine	2·33	2·0	2·0	3·0	2·39	3·0	2·8	1·3	2·17	1·8	2·5	2·3
Barbiturates	2·23	2·3	1·9	2·5	2·01	2·0	2·2	1·8	2·00	2·4	1·9	1·7
Street methadone	1·86	2·5	1·7	1·4	2·08	1·8	2·3	2·3	1·87	1·6	1·9	2·0
Alcohol	1·40	1·9	2·4	NA	1·93	2·3	1·9	1·6	2·21	2·2	2·4	2·1
Ketamine	2·00	2·1	1·7	2·1	1·54	1·9	1·7	1·0	1·69	2·0	1·5	1·5
Benzodiazepines	1·63	1·5	1·7	1·8	1·83	1·7	2·1	1·8	1·65	2·0	1·5	1·5
Amphetamine	1·81	1·3	1·8	2·4	1·67	2·0	1·9	1·1	1·50	1·4	1·5	1·6
Tobacco	1·24	0·9	2·9	0	2·21	2·3	2·6	1·8	1·42	0·8	1·1	2·4
Buprenorphine	1·60	1·2	1·3	2·3	1·64	2·0	1·5	1·5	1·49	1·6	1·5	1·4
Cannabis	0·99	0·9	2·1	0	1·51	1·9	1·7	0·8	1·50	1·7	1·3	1·5
Solvents	1·28	2·1	1·7	0	1·01	1·7	1·2	0·1	1·52	1·9	1·5	1·2
4-MTA	1·44	2·2	2·1	0	1·30	1·0	1·7	0·8	1·06	1·2	1·0	1·0
LSD	1·13	1·7	1·4	0·3	1·23	2·2	1·1	0·3	1·32	1·6	1·3	1·1
Methylphenidate	1·32	1·2	1·3	1·6	1·25	1·4	1·3	1·0	0·97	1·1	0·8	1·1
Anabolic steroids	1·45	0·8	2·0	1·7	0·88	1·1	0·8	0·8	1·13	1·3	0·8	1·3
GHB	0·86	1·4	1·2	0	1·19	1·4	1·1	1·1	1·30	1·4	1·3	1·2
Ecstasy	1·05	1·6	1·6	0	1·13	1·5	1·2	0·7	1·09	1·2	1·0	1·1
Alkyl nitrites	0·93	1·6	0·9	0·3	0·87	1·6	0·7	0·3	0·97	0·8	0·7	1·4
Khat	0·50	0·3	1·2	0	1·04	1·6	1·2	0·3	0·85	0·7	1·1	0·8

Table 3: Mean independent group scores in each of the three categories of harm, for 20 substances, ranked by their overall score, and mean scores for each of the three subscales

Figure 3. Mean Independent group scores in each of the three categories of harm, for 20 substances, ranked by their overall scores, and mean scores for each of three sub scales. From: Nutt, D., King, L. A., Saulsbury, W., & Blakemore, C. (2007). Development of a rational scale to assess the harm of drugs of potential misuse. *The Lancet*, *369*(9566), 1047–1053. http://doi.org/10.1016/S0140-6736(07)60464-4

Summary: While aggressive rhetoric has plagued medicinal *Cannabis* use, evidence of relative harmlessness, as compared to other drugs, is pervasive. The imperceptible LD_{50} of the cannabinoids, coupled to a clear historical record of anecdotal safety, contributes to a compelling likelihood that the cannabinoids are the safest class of medicinal compounds yet studied. The relative safety profile of *Cannabis* alone might be seen as strong motivation for further research.

For additional information see sections (6) adverse reactions in humans, (7) dependence potential, and (8) abuse potential within this document.

(15) Licit production, consumption and international trade, (16) Illicit manufacture and traffic, and related information, (17) Current international controls and their impact, (18) Current and past national controls, and (19) Other medical and scientific matters relevant for a recommendation on the scheduling of the substance (These sections are grouped and discussed together because the research is inter-related).

Introduction

The current international controls are the strictest controls possible for narcotic drugs under the Single Convention; stricter control than that affected through being placed in

Schedules I and IV of the Single Convention is not possible. Since the 1970s, some countries have decriminalized, depenalized, condoned, or legalized the possession of *Cannabis* and sometimes also the distribution, cultivation, and manufacturing.

There are several themes that underlie the disparities of the history of international drug control and influenced the development and implementation of the three conventions [63,362]. International drug control regime began with the idea to prohibit drug production and use for non-medical or non-scientific purposes. The focus was set on controlling the supply of drugs, while also imposing penalizations on illicit drug producers, traffickers, dealers, and users. Only recently have other issues such as public health concerns, and user harm reduction options begun to be considered.

Many outside social factors, not directly related to drug control, have also influenced international drug control (e.g. racism, the economy, politics, global trade, war, arms control initiatives, the Cold War, and other various corporate agendas)[63,64,363]. Since the beginning of international drug control efforts, the U.S. has been a key player in many of the major decisions. From prohibition, to the "war on drugs", the U.S. has had a primary influence in almost all multilateral negotiations. Most influential have been the powerful people involved, especially those who have held positions of power at the right moments in history, who were able to steer the international drug control regime in a particular direction[63].

In order to better understand current international controls, it is important to understand the context that created the current situation. Efforts to reschedule *Cannabis* are marked by a storied history that includes barriers to research and the spread of sensationalistic reports. A short review of International and national controls are found below.

1912 Hague Convention

The control of opium was the focus of the 1912 Hague Convention. The treaty provided that the use of opium should be restricted to medical and scientific purposes, this established a principle which would guide the foundation of all other related international treaties and agreements[349,364-366]. The Convention did not officially address *Cannabis*, however the delegates did sign a protocol, which discussed the "hemp question" and stated that it should be studied from a "scientific point of view." Italy and the U.S. sought to bring *Cannabis* production and trafficking under international control, despite the U.S. having no domestic laws of its own for *Cannabis*.

1925 Geneva Convention

After World War I, the U.S. pressured the League of Nations to have another convention. South Africa, Egypt, and Turkey proposed that *Cannabis* be included in the list of narcotics covered by the convention. With the U.S. and Canada also strongly supporting the idea that *Cannabis* be covered, for the first time *Cannabis* was formally discussed at

the convention.

The matter was delegated to a subcommittee, composed of Western countries in which *Cannabis* use was virtually unknown and had no domestic *Cannabis* laws at the time. Information used to guide these decisions was largely based on sensationalistic, popular writings of the era, and not on any scientific or medical information. This influential, popular fiction included unfounded statements about how *Cannabis* use would turn a nation's "black population into an unruly mob" and that use of hashish or *Cannabis* resin ultimately resulted in insanity[364]. Hence, the subcommittee formed of nations' representatives – whom had no practical knowledge or experience with *Cannabis* use domestically – strongly supported a complete prohibition of *Cannabis* and its constituent resin. Based on the recommendation of complete prohibition, another subcommittee drafted provisions requiring the parties to:

- Impose domestic controls over tinctures and extracts of Indian hemp.
- Impose export/import control over Indian hemp and resin.
- Prohibit export of resin to countries that prohibit its use, or if importing is allowed, to require the country to issue a special permit certificate stating that the import was approved for medical and scientific use, and would not be re-exported.
- Prevent the illicit international traffic in Indian hemp, as well as the resin or extracts thereof.

These provisions were ultimately adopted and included in the convention (the Wootton report) and caused the prohibition of *Cannabis* from "the top down". The 1925 convention did not prohibit the domestic cultivation, production or distribution of hemp. Despite the convention allowing domestic regulation of medical *Cannabis* and its preparations, Western countries enacted legislation to prohibit *Cannabis* while providing no evidence of serious domestic *Cannabis* problems.

During this time, *Cannabis* prohibition was enacted by Great Britain with the Dangerous Drug Act of 1925 and Canada added *Cannabis* to its regulated substances list under their Opium and Narcotics drug act of 1929. Thus began the prohibition of *Cannabis* in the Western world.

1931 and 1936 Geneva Conventions

The import control system that the 1925 Geneva Convention put in place only partially helped the problem, since drugs continued to be smuggled in through various non-signatory countries. In 1931, the Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs was created which set limits on the manufacture and distribution of cocaine, morphine, and heroin[362].

One of the biggest developments in U.S. drug policy came with the creation of the

Federal Bureau of Narcotics in 1930. Their first Commissioner, Harry J. Anslinger, who held the position for 33 years, is widely known for having one of the biggest impacts on the development of U.S. drug policy. His devoted stance on maintaining prohibition and government control of drugs not only affected U.S. policy, but also international drug control[367]. It was Anslinger that purposely transformed the language – and so the plant *Cannabis* became the scourge "marihuana", a non-scientific term.

The Advisory Committee on Traffic in Opium noted that a "smuggling trade" had sprung up between Canada and the U.S. The committee suggested that as coca and opium derivatives availability were restricted, addicts would resort to *Cannabis*. Therefore, marijuana should be closely monitored (Wootton report).

The U.S. submitted memorandums, which described "a widespread habitual use of marihuana" and "the alarming influence of [marihuana] addiction" on criminality. By this time, 34 of 47 states had legislation prohibiting *Cannabis*. The committee's concern led to a special assessment of *Cannabis*, by a subcommittee on Indian hemp, with the U.S. representative chairman. The subcommittee conducted a critical review of the literature that lasted several years, but issued no report because there was not enough scientific or medical information to support the relationship between the use of either *Cannabis* or its extracts on crime, insanity, addiction, or transitions to other "harder" drugs such as heroin.

The Period Between 1936-1961

At the end of the 1940s, the disparity of treaty provisions was creating confusion. At the suggestion of the U.S., the (UN) Commission on Narcotic Drugs (CND) was formed and undertook to consolidate all previous treaties.

During this time, *Cannabis* started to receive considerable attention and reports were submitted from the U.S. and a number of non-Western countries indicating increasing issues with *Cannabis*. By 1954, WHO was advising the CND that marihuana and marihuana preparations no longer served any useful medical purpose (Wooton Report). The CND consolidated the information from the WHO advisors and non-scientific reports from various countries and in 1961, the CND had a draft to be considered for a convention. The draft stated that *Cannabis* was a dangerous narcotic, similar to the most dangerous opiates.

1961 Single Convention

The 1961 Single Convention on Narcotic Drugs (Single Convention) strengthened and maintained existing controls, requiring licensing, reporting on national estimates of drug requirements, limits on production and manufacturing, among other requirements. The convention classified substances within four schedules. The most stringent levels applied to Schedules I and IV, with Schedule IV suggesting prohibition of the drug.

At the urging of the U.S., *Cannabis* and *Cannabis* resin were placed not only in Schedule I but also in Schedule IV, allegedly because its abuse was widespread and WHO had determined the medical uses of *Cannabis* to be obsolete. While *Cannabis* was listed as Schedule IV (most restrictive), '*Cannabis* tinctures' and 'extracts' were only placed into Schedule I.

Schedule IV substances under the convention:

- May, but are not required to be, completely prohibited (activities such as cultivation, production, manufacturing, and distribution). A party must prohibit the manufacture, export and import of, trade in, possession or use a Schedule IV drug, except for amounts that are necessary for medical and scientific research including clinical trials. (This requirement applies only if the country or party believes "the prevailing conditions in its country render [such prohibition] the most appropriate means of protecting the public health and welfare").

- Countries that permit cultivation of these substances are required to set up a national monopoly that would take possession of and distribute the crops.

- Requires parties to enact punitive domestic legislation, so that activities contrary to the treaty are 'punishable offences' and that 'serious offences' would be held to 'adequate punishment particularly by imprisonment or other penalties of deprivation of liberty'.

1971 Convention

Drug abuse continued to increase after 1961, with substances that were not covered by the Single Convention. Hence, the result was the Convention on Psychotropic Substances of 1971 (1971 Convention).

Similar to the Single Convention, the 1971 Convention classified substances into four schedules, with the organization of those schedules being *completely* different from the Single Convention. Under the 1971 Convention, Schedule *I* became the *most* restrictive classification, while under the Single Convention Schedule IV was the most restrictive.

Tetrahydrocannabinols (THC and related compounds) were initially placed in Schedule I. Dronabinol (Δ^9-THC) was moved to Schedule II in 1991. Dronabinol is a Schedule III substance in the U.S. (a similar Scheduling system to the 1971 Convention), and is available by prescription. In the U.S., dronabinol is Schedule III, while *Cannabis* remains in Schedule I. In 2014, the CND did not approve the proposal of WHO to move dronabinol to Schedule III of the 1971 Convention.

The 1971 Convention required parties to treat acts contrary to the treaty as punishable offenses, as described in the Single Convention. However, Article 22 allowed nations to provide treatment, education, aftercare, rehabilitation, and social re-integration as

alternatives to or in addition to punishments (i.e., incarceration or deprivation of liberty) for individual drug abusers.

1988 Convention

Since drug trafficking continued to rise unabated, another treaty – the 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychoactive Substances – was adopted. The focus of the 1988 Convention was combating international drug trafficking.

The controversial and unique issue with this convention arised from its provision that countries must establish a criminal offence for possession for personal use – that is, the 1988 Convention viewed the drug user as *part* of the criminal enterprise – declaring "drug users are also to be considered criminals.[362]" Despite this provision, alternatives continued to be used, as permitted by the Convention. These alternatives include treatment, education, etc. In some cases, these alternatives were in *addition* to punitive sanctions while in other cases, alternatives could only be applied with punitive measures in more serious offences.

The Conventions and Medical Cannabis Use

The 1961 and 1971 Conventions offered some choices or options for parties regarding *Cannabis* controls. The conventions did not specify in detail what a nation must do to implement their provisions.

Another example of the choices regarding *Cannabis* control is that the enactment of penalties against non-authorized *Cannabis* users are limited by the constitutionality of the party; the obligations to the conventions are subject to "constitutional limitations." According to both the Single Convention and the 1971 Convention, if a national or federal court ruled that an individual had a constitutional right to medical *Cannabis* access, then that nation or party would be relieved of requirements of the Convention requiring punishment.

Do International Treaties Allow Cannabis Medicines to be Legally Available?

The Single Convention governs the conditions under which a complex preparation derived from *Cannabis* plant could be available for medical use. Single natural cannabinoids and new synthetic cannabinoids or cannabimimetic agents would be governed by the 1971 Convention. Both conventions allow for the medical use of *Cannabis* and cannabinoids. However, the present control status of *Cannabis* and cannabinoids makes such use very difficult or impossible in many countries. The presence of *Cannabis* in Schedule IV of the 1961 Convention is considered by many parties as a recommendation to also prohibit and punish its medical use.

Where Are We Now? Countries and their Medical Cannabis Controls

At present there are forty states in the U.S. and Canada, Israel, Netherlands, Czech Republic, Croatia, Mexico, Chile, Uruguay, Poland, Finland, Norway, Germany, Jamaica, Australia, Italy, Columbia, and Switzerland where *Cannabis* and *Cannabis* products are available to their citizens. These countries have taken different approaches to distribute *Cannabis* and *Cannabis* products to their populations. Some of the approved *Cannabis* products are not covered by insurance providers and therefor their actual consumption remains minimal. In Sri Lanka, *Cannabis* has been used legally in Ayurvedic medicine. In most other countries, patients can only obtain their medicine from the illicit market.

North America

Canada

In Canada, about 50,000 patients across the country are authorized to use medical *Cannabis*. This number is expected to reach upwards of 400,000 over the next ten years. In 1999, Health Canada indicated that it would support and fund controlled clinical trials investigating the potential of *Cannabis* as a therapeutic agent. The investigation of the safety and efficacy of smoked research grade *Cannabis* in such trials was a priority due to public perception that smoked herbal *Cannabis* was effective and patients in Canada were currently using *Cannabis* in that form. In July 2001, Health Canada announced the first trial to be conducted involving patients with chronic neuropathic pain.

Health Canada can authorize patients to use medical *Cannabis* pursuant to section 56 of the Controlled Drugs and Substances Act (CDSA). Under section 56, the Minister of health has discretionary power to grant an exemption from the application of any or all part of the CDSA or its regulations; if the minister believes the exemption is necessary for medical or scientific purposes or is otherwise in public interest.

In 2000, Health Canada awarded a five-year $5.8 million contract to Prairie Plant Systems to grow and produce research quality *Cannabis*. The first crop, grown underground in an abandoned copper mine, became available in early 2002, and was distributed to researchers and qualified patients. To satisfy its obligations under the Single Convention, Canada established a national agency, the Office of Cannabis Medical Access (now Marihuana Medical Access Division) to take control and supervise distribution.

In the year 2000, the Ontario Court of Appeal also ruled that the laws prohibiting personal possession and use of *Cannabis*, even for medical purposes, was unconstitutional. The court ruled that a prohibition against possession and cultivation for medical use was not necessary to fulfill Canada's obligation under the Single

Convention. It further ruled that the lack of an adequate legislative standard for determining medical necessity under section 56 and that the discretion of the minister "did not accord with the principles of fundamental justice"[349]. As a result, the court declared the entire prohibition against *Cannabis* for medical use was invalid but the ruling was suspended for one year to allow the government to develop a defined regulatory process through which patients could be authorized to use *Cannabis* in cases of medical necessity.

Following this ruling, Health Canada issued regulations called the Marihuana Medical Access Regulations (MMAR), which were designed to make the medical exemption process more transparent.

In 2014, the MMAR were replaced by the Marihuana for Medical Purposes Regulations (MMPR). This is the set of rules for growing, buying, and selling medical *Cannabis* in Canada. It outlines a system for doctors, patients, and commercial growers (licensed producers). In order to access *Cannabis* for medical purposes, individuals must have the support of a healthcare practitioner and have him/her complete a medical document that explains the daily amount of *Cannabis* required. With that medical document, individuals can register with one of the licensed producers identified on the Health Canada website. The MMPR requires licensed producers to ensure the safe distribution of *Cannabis*. As such, licensed producers are only permitted to provide *Cannabis* to registered clients and this *Cannabis* must be securely shipped directly to the client or an individual responsible for the client.

In February 2016, a court ruling struck down MMPR provisions restricting the rights of medical *Cannabis* patients to produce their own medical *Cannabis*. Such production was possible under the previous rules (MMAR). The Government promised to respond to this ruling within six months to make sure Canadians who require *Cannabis* for medical purposes have appropriate access.

Mexico

In Mexico, *Cannabis* and *Cannabis* products are used by many patients for medical purposes. However, such use is not legal. Since 1994, Mexico does not have criminal penalties for the use of psychoactive substances but it is administratively sanctioned with fines. The possession for consumption is considered a crime. In the event that a person possesses less than the maximum amount (5 grams in the case of *Cannabis*), then it will not result in imprisonment, with the exception of places such as schools and prisons, amongst others.

Currently, there is a debate to propose reforms to this legislation. In August 2015, a judge authorized the importation of a substance derived from *Cannabis* to be used as a medical instrument in an 8-year-old girl diagnosed with epilepsy – a substance prohibited by

Mexico's General Health Act. Possession and supply for medical purposes continues to be a crime, but this court precedent has opened public debate.

One of the arguments in the debate with the Federal Congress is to increase the non-criminalized possession of *Cannabis* from 5 to 30g and also to authorize the prescription of medical *Cannabis*. In this trend of changes, the movement of *Cannabis* users has emphasized that the decriminalization of *Cannabis* use and the possibility of self-cultivation is a way to weaken drug trafficking.

United States

More than 2 million patients have access to medical *Cannabis* and *Cannabis* products under state laws. More than 40 U.S. states have a *Cannabis* access program for medical use. Many of these states have adopted standards for regulating *Cannabis* products in these markets as botanical standards with appropriate monographs. A recent U.S. Pharmacopoeia (USP) meeting cite the American Herbal Pharmacopoeia (AHP) *Cannabis* monograph as the current standard for regulating *Cannabis* as a medicine in the U.S. The USP cannot release an official monograph for *Cannabis* until it is rescheduled to a much less restrictive category[368].

Over the past decade, U.S national polls have consistently ranked support for medical *Cannabis* among Americans at around 80%. Various efforts to reschedule *Cannabis* in the U.S. based on medical and scientific information have been stymied. A medical marijuana patient advocacy group, Americans for Safe Access (ASA), filed a petition with the federal court of appeals to reclassify *Cannabis* for medical use. Plaintiffs in the case ASA v. DEA are requesting a rehearing before the original panel, as well as seeking full (en banc) review by the U.S. Court of Appeals for the District of Columbia (D.C.) Circuit. The D.C. Circuit granted plaintiffs standing -- the right to sue the federal government to reclassify *Cannabis* -- but, in a 2-1 ruling, denied the appeal on the merits by setting a new standard for assessing medical efficacy. While *Cannabis* remains a Schedule I drug, this new standard is virtually impossible to meet.

ASA cited more than 200 peer-reviewed studies in its appeal, but the D.C. Circuit held that plaintiffs must produce evidence from Phase II and Phase III clinical trials -- usually reserved for companies trying to bring a new drug to market -- in order to show *Cannabis'* medical efficacy. Long term, Phase II and III studies on medical *Cannabis* will simply not be approved by the DEA or the NIDA under the current standards regulating their national monopoly on *Cannabis* produced for clinical research, unless *Cannabis* were to be rescheduled under the Conventions.

In 2002, the Coalition for Rescheduling *Cannabis*, made up of several individuals and organizations including ASA, filed a petition to reclassify *Cannabis* for medical use. That petition was denied by the DEA in July 2011, after ASA sued the Obama Administration for unreasonably delaying the answer. The appeal to the D.C. Circuit was the first time in

nearly 20 years that a federal court has reviewed the issue of whether adequate scientific evidence exists to reclassify *Cannabis*. Before the January ruling, the D.C. Circuit had never granted plaintiffs the right to sue when seeking reclassification of *Cannabis*.

Patient advocates claim that *Cannabis* is treated unlike any other controlled substance and that politics have inappropriately dominated over medical science on this issue. Advocates point to a research approval process for *Cannabis*, controlled by NIDA, which is unique, overly rigorous, and effectively hinders meaningful pre-clinical and therapeutic research. In its appeal brief, ASA argued that the DEA has no "license to apply different criteria to marijuana than to other drugs, ignore critical scientific data, misrepresent social science research, or rely upon unsubstantiated assumptions, as the DEA has done in this case."

Patient advocacy groups such as ASA, continue to put pressure on the U.S. Presidential administration, but are also lobbying Members of Congress to reclassify *Cannabis* for medical use. The Compassionate Access, Research Expansion, and Respect for States (CARERs) Act has also been introduced, which in addition to rescheduling *Cannabis* would allow states to establish *Cannabis* access laws and product safety regulations without interference by the federal government, and would remove current obstacles to research.

Europe

Meanwhile in Western Europe, medicinal (pharmaceutical grade) herbal *Cannabis* (*Cannabis* flos) is available as an unregistered medicine for patients in The Netherlands, Germany, Italy, Finland, Norway, and Switzerland, with a valid prescription from a doctor. Politicians/parliaments in Belgium, the UK, France, Austria, and the other Scandinavian countries (Denmark, Sweden and Norway) are still debating whether *Cannabis* should be legalized as a medicine.

The central government of Italy allows local production of medicinal *Cannabis* upon a positive decision of regional governments. Norway now allows patients to bring legally obtained medicinal *Cannabis* home from Holland or other European countries that are signatories of the so-called "Schengen agreement."

The governments of Italy, Luxembourg, Portugal, and Spain do not consider personal consumption a crime and many other activities (transportation, acquisition, etc.) are only subject to administrative sanctions. Other nations, such as Belgium, are also considering reform efforts such as decriminalization.

Germany revised its *Cannabis* laws, and a new draft law will soon be discussed in the Bundestag, the German parliament. This draft is assumed to be accepted quickly. The core of this revised law is to appropriately research medicinal *Cannabis*, medicinal *Cannabis* derivatives and other cannabinoid medicines over three years, by allowing

patients access to these products on the basis of a doctor's prescription (any condition is allowed). Patients who agree to take part in this research will get their prescribed products fully reimbursed during those three years. Results of this broad study will be used in 2019 to define the conditions for which cannabinoid products will be allowed and reimbursed by the German healthcare system.

Spain and Portugal are holding a slightly different position. Spain tolerates production by so-called Social Clubs and decriminalized possession of *Cannabis*; however, health care professionals in Spain are not satisfied with this situation because of lack of quality control. Portugal also decriminalized possession of *Cannabis*.

Bedrocan BV in The Netherlands is the main licensed producer of *Cannabis* flos in Europe under a license of and contract with the Dutch government. It is a 100% privately owned company with a long history in *Cannabis* production since 1992. The company has now two facilities in the north of the country with an annual production capacity of 1500 kilogram in five fully standardized distinct varieties. The company is ISO 9001-2008 certified and expects to be Good Manufacturing Practices (GMP) certified for production of active pharmaceutical ingredients (API) in Q3 2016. Every 5 years the Dutch government issues an RFP for production and packaging of *Cannabis* flos.

Besides Bedrocan BV, there are four more licensed producers in Western Europe: GW Pharmaceuticals (UK), the Austrian government agency AGES, the pharmaceutical department of the Italian Army in Florence (Italy), and a producer in Switzerland.

AGES is producing approximately 150 kilograms annually in a state owned greenhouse in Vienna, exclusively for the German bio-pharmaceutical company Bionorica. This company is producing pure THC under the trade name Dronabinol for the German and Austrian market.

The Italian Army started testing their facility in 2015. The first output of *Cannabis* flos is expected in Q3 2016. The capacity of this facility is estimated at 100 kg annually. Their source of *Cannabis* genetics is the Italian government agricultural research institute CREA located in Rovigo. They produce only one variety with equal levels of THC/CBD.

Distribution of medicinal *Cannabis* in all countries is only allowed through the regular pharmaceutical infrastructure (pharmaceutical wholesalers and local pharmacies). Countries allowing production are all in compliance with the UN regulations, meaning that production, quality control, and wholesale distribution only happens under a state monopoly. This monopoly has to be maintained by a state-appointed *Cannabis* agency responsible for:

- license *Cannabis* production

- take physical possession of *Cannabis* after it has been produced
- perform quality control on the products by third party testing
- bring the product to the regular distribution channel (pharmacies)
- make the product available for research and production of medicines

Production of derivatives of *Cannabis* is seen by governments as production of (unregistered) medicines and should therefore take place in a dedicated facility. Currently two pharmacies in The Netherlands have started production of standardized *Cannabis* oil (extract dissolved in a food grade oil).

Other European Countries

Bulgaria

According to the Bulgarian Narcotics and Precursors Law, there is no differentiation between medical use and recreational use. The possession and cultivation of *Cannabis* could lead to 2 to 6 years in prison. Since the last edition of the law, there will be no exceptions for using *Cannabis* for medical purposes at all. There were recently two cases of people with suspended sentence for using *Cannabis* for their illnesses (one MS patient and one leukemia patient).

Croatia

In October 2015, Croatia authorized the use of *Cannabis* and *Cannabis* products for medical purposes to be distributes through pharmacies. These products can be prescribed by general practitioners following the recommendation by a specialist.

Czech Republic

In 2008, the Czech Republic decriminalized *Cannabis* for individual possession and cultivation. In 2012, medical *Cannabis* legislation was passed. Since 2014, medical *Cannabis* has been available under electronic prescription dispensed through pharmacies that is imported from the Netherlands. The cultivation of *Cannabis* in the Czech Republic started in 2015 through licensed producer. The Czech situation is similar to the Dutch. Elkoplast S.R.O. is producing under a government license and contract since late 2015. The production facility is equipped and staffed by Bedrocan BV and produces only one variety for the time being (var. *Bedrocan*). In 2016, Elkoplast is licensed and contracted for production of 40 kg.

Former Yugoslav Republic of Macedonia

In the Republic of Macedonia, production, possession, selling, and using of *Cannabi*s is still illegal. There is a draft law for legalization of *Cannabis* for medical use. The law already passed some parliamentary commissions and is currently in phase for

amendments discussions. One amendment is to allow for patients and caregivers to cultivate *Cannabis*.

Poland

Cannabis and *Cannabis* products are available by import. A new law is currently being debated in the Polish Parliament.

Serbia

Cannabis oil use for medical purposes has been advocated for since 2014. Nevertheless, *Cannabis* based medicines were not regulated until January 2016, two of which were based on synthetic cannabinoids and only one based on *Cannabis*. Patients will receive them free of charge with doctor's prescription at the expense of the National Health Insurance Fund (NHIF). "Dronabinol" will be used for the treatment of weight loss in HIV and AIDS patients, as well as for nausea caused by chemotherapy. "Nabilone", a synthetic THC-like substance, will be applied for the treatment of nausea in patients receiving chemotherapy. Nabiximols in the form of spray, which contains natural THC, will be given to patients with multiple sclerosis to relieve spasm, only when the spasm is not adequately controlled by conventional therapy. Request for registration of these drugs to the Medicines and Medical Devices Agency, was filed, but they are not expected in pharmacies until mid-year. The doctors of various specialties will participate in determining the indication for the use of these drugs and submit them to the Ministry of Health (MoH). A list of certified doctors who will be authorized to prescribe these drugs will be established. The MoH Commission concluded that oil from *Cannabis* should not be legalized. One of the arguments was that there are no defined standards for production and quality of the oil.

Slovenia

For almost two years medicines based exclusively on synthetic THC and CBD have been available in pharmacies only with a doctor's prescription. The debate on *Cannabis* policy is active at the Parliamentary level.

Central and South America and the Caribbean

Some countries in these regions already allow for medical use of *Cannabis* and *Cannabis* products. However, the patients in most countries concerned can only receive their medicine from illegal sources.

Argentina

In Argentina, there is currently no regulation for the medical use of *Cannabis*. There is a precedent related to a court ruling that approved the importation of nabiximols for an HIV patient who suffered from severe neuropathy. The ruling included a statement

stressing that the medicinal uses of *Cannabis* are not allowed in the country but in special cases, in what is referred to as "the compassionate use of medical products," individuals are allowed to import with authorization and/or use medical products that are non-commercialized. Such cases included those clinical situations in which the individual is incapacitated or the quality of life is deteriorating and conventional therapy is not effective or intolerance occurs to existing treatments.

Brazil

Brazil criminalizes the illegal possession of drugs, with no specific amount or limit. A judge will determine if the possession is for personal use or intended for trafficking based on the type of drug, the quantity, and the person's background. A law that does not penalize consumption and rejects the imprisonment of consumers was introduced in 2006. The cultivation for personal use is also not criminalized. In January 2015, Brazil's Health Surveillance Agency removed CBD from the list of banned substances.

Chile

Since 2013, Chile began to recognize the therapeutic potential of drugs derived from *Cannabis*. This is in part by the pressure from the public and support from the Medical College of Chile, which has offered *Cannabis* drugs to patients suffering from chronic pain or diseases refractory to other treatments. From there, the Public Health Institute (Instituto de Salud Pública or ISP in Spanish) has issued resolutions approving the entry of drugs with cannabinoid compounds for people who have requested it. In December 2015, President Bachelet signed a decree stating that the ISP may authorize and control the use of *Cannabis*, *Cannabis* resin and *Cannabis* tinctures for the manufacturing of pharmaceutical products for human consumption. This decree was given to the health committee of the government. There was a modification of Decrees 404 and 405, which allowed the prescription of pharmaceutical products containing derivatives of *Cannabis*.

The first municipal *Cannabis* farm has been approved for therapeutic purposes in Chile. It is a pilot project called "Compassionate Use of Cannabis Oil to Cure Pain in Cancer Patients." The initiative, implemented by the Daya Foundation and the Municipality of La Florida, was made possible after the Agriculture and Livestock Services -after consulting the Administration, the Ministry of Interior through the National Service for the Prevention and Rehabilitation Consumption of Drug and Alcohol (PATH), and the Institute of Health- authorized the plantation. The project, which began with the planting of 850 seeds from four distinct and different types of plants brought from Holland (Durga Mata II, Wappa, Icecream and Pandora), aims to implement medicinal oil therapies for the management of pain relief in 200 cancer patients, 100 health service users from the commune of La Florida and 100 beneficiaries of the Daya Foundation. Oil and resin were chosen because it is a natural extract of *Cannabis* with which the components are concentrated and therapeutically useful, and is a non-toxic form of consumption and proper dosing is easier to control.

This project has support from the University of Valparaiso, Chile Pharmacopoeia and Knop Laboratories. Valparaiso University and the Chilean Pharmacopoeia have made available to the project its expertise and scientific techniques for case studies of *Cannabis* oil. They perform quality control, set parameters, and standardize procedures for obtaining a reliable prepared and safe form, which is currently being produced by Knop Laboratories (www.fundaciondaya.org).

However, there is not enough regulated production, which may be responsible for the increase in cases of fraud where a fake product is marketed as therapeutic *Cannabis* oil, exposing users to adulterated products. It is then expected that the pilot driven by Foundation Daya may open the way to effective regulation and allow access to medicinal *Cannabis* to the entire population that requires it.

Colombia

In December of 2015, medical *Cannabis* was legalized through a decree governing the cultivation, processing, importation, and exportation of *Cannabis* and its derivatives for therapeutic purposes. This created licenses for the possession of seeds for cultivation purposes, which should be used exclusively for therapeutic and scientific use. Medical use was already permitted under the law since 1986, but its application was pending since there was a lack of regulation. Public consumption and commercialization are prohibited although possession up to 20g for personal consumption has been decriminalized since 2012. It is legal to grow up to 20 *Cannabis* plants and it is possible to buy medicinal products, which have the leaf as its base ingredient. For cultivators who are growing more than 20 plants, a license is given as long as they demonstrate the contracts between the producers and the companies involved in the drug production. There is criticism that it is very difficult for small producers, indigenous people, and/or farmers to meet conditions, which puts their livelihoods at risk.

Costa Rica

Possession or consumption are not considered crimes. Only in the case that there is evidence that it will ultimately be used for commercialization, one can be condemned to 8-12 years of imprisonment. There are currently several proposals for laws ranging from making marijuana available for medicinal use, allowing the consumption as a treatment for certain problems and to legalize the cultivation for personal use, which are all still hotly debated.

Ecuador

From 2008 to 2015, Ecuador has gone through a series of reforms that has led them from a regime highly punitive to the granting of pardons of small traffickers to one where they released a large number of persons deprived of liberty by drug charges. Cultivation for personal use is not penalized. Although possession is typified as a crime, if it is less than

10 g and for personal use, it is not punished.

Jamaica

Since 1972, Jamaican scientists at the University of the West Indies (UWI) Department of Pharmacology have studied the properties of *Cannabis*; developing a number of products to treat glaucoma, asthma, and motion sickness.

Following the Conventions, Professor Manley West and Dr. Lockhart were among the first to develop new *Cannabis* products. There was still no medicinal industry per se, so beyond the immediate matter required for their research and development, there was no real widespread demand of *Cannabis* for medicinal purposes.

All through history, the Caribbean community have used indigenous herbs for treatment of specific ailments and this case specifically *Cannabis* as a traditional cure. Currently the legal changes occurring in Jamaica are likely to be adopted in some legislative form in other Caribbean Community countries (CARICOM).

License growers will have to be compliant to regulations and cultivation practices whether for outdoors or indoor grow and will also have to meet set standards for approval and certification as medical *Cannabis*.

In April 2015, Jamaica became the first Caribbean nation to decriminalize *Cannabis* through the amendment of their Dangerous Drug Act. In 2016, Jamaica will establish a *Cannabis* licensing authority (CLA) that was authorized by the Jamaican government. The CLA will issue six categories of licenses that will become the framework of a medicinal *Cannabis* industry.

Presently preparations are ongoing to adopt classification and standardization principles for a newly regulated medicinal *Cannabis* industry soon to be launched in Jamaica. The Caribbean and in particular Jamaica is well known for producing ‘ital grade ganja’ which is grown naturally in humous soil or equivalent, free of any harmful chemicals, or animal fertilizers.

Medicinal application for Caribbean region with *Cannabis* has always been through traditional means. The methods most often used are smoking, vapor inhalation, ointments, and tinctures. However, modern approach to pharmaceutical medical *Cannabis* application for cancer treatment such as medicinal dissolvable sublingual preparations, medicinal transdermal patch, *Cannabis* oral mucosal spray, medicinal liquid shots, medicinal buds and vapor are all on the cards for Jamaican development of medicinal *Cannabis*.

Uruguay

Through the adoption of Law 19.172, Uruguay became the first country in which the state assumes the regulation of *Cannabis*, not only for medical purposes but also for recreational use, being responsible for its production, storage, and sale. Under the guise of public health, this regulation allows better characterization of consumers, development and reduction of risks associated with an underground market, providing better options for both recreational and medical drug users, sustainable development and preventive policies to incorporate small farmers in projects which prevents their migration to the city and thus into impoverished areas.

The agency responsible for the regulation is the "Institute of Regulation and Control of Cannabis" (IRCCA). The acquisition of *Cannabis* is allowed in the following ways: self-cultivation (up to six plants per person), in pharmacies (with a maximum purchase of 40g monthly), through the Ministry of Health in the case of therapeutic use, or through *Cannabis* clubs (associations who cultivate for their members).

Taxes collected are used for the control of legislation, treatment for people with addictions, educational campaigns, and preventive measures to avoid problematic substance use and investment in social services.

Asia

Israel

Israel's national Medical Cannabis program evolved over the last 15 years from an activist efforts to a form of a national program serving over 25,000 patients with *Cannabis* grown by eight cultivation groups. Israel is the third country in the world to establish a National Medical Cannabis Program/Agency, after Canada and the Netherlands. The National Medical Cannabis Agency was established in 2011 as part of the Ministry of Health as required by the 1961 Convention.

Cannabis is allowed for patients that have received a prescription to use the medicine from a Doctor that specializes in the patient's disease. Patients are not allowed to grow *Cannabis* for medical use. *Cannabis, Cannabis* oil and extracts are allowed to be consumed by smoking but edible products (i.e., food infused with *Cannabis)* are not allowed. The quality assurance and quality control requirements require that each crop is properly examined and tested before it reaches the patient, all laboratory testing results are sent to the Agency.

Sri Lanka

Cannabis has been used in Ayurvedic medicine. It is obtained for such medical use from *Cannabis* seized by the law enforcement authorities in Sri Lanka.

Oceania

Australia

In February 2016, the Australian federal parliament passed the Narcotic Drugs Amendment Bill. This will allow a newly formed Federal Office of Drug Control to issue licenses for the cultivation of *Cannabis* for manufacture into medicinal *Cannabis* products, and for research into the *Cannabis* plant to be used for medicinal purposes.

There will be a range of strict requirements to be met for those seeking licenses. These relate to criminality checks and demonstrated capacity to successfully and securely grow *Cannabis* and manufacture *Cannabis*-related products.

Cannabis products manufactured via the licensing system will need to be approved by the Australian Therapeutic Goods Administration and will be obtained by patients via prescription by doctors and pickup from pharmacies.

In preparation for this new system, the government has moved to reschedule *Cannabis*, *Cannabis* extracts and THC (when used for therapeutic purposes). The proposed rescheduling is from Schedule 9 (Prohibited Drug) to Schedule 8 (Controlled Drug) allowing prescription by authorized doctors. This rescheduling is anticipated to be implemented mid-2016.

International and National Barriers to Safe Access

There are still significant barriers to medical *Cannabis*. There exists a lack of high-level education amongst health care professionals, and lack of clear clinical research still keeps a majority of medical doctors away from prescribing *Cannabis* as a medicine. In conjunction, many health insurance companies do not reimburse *Cannabis,* even as prescribed by a doctor.

The financial burden for a majority of patients is arguably too high. Even in countries with a relaxed *Cannabis* policies, prices are prohibitive to proper access. In The Netherlands, patients are now paying approximately $10-12 USD per gram, however in Italy and Germany prices go up to sometimes $25 USD per gram. The average use in The Netherlands is now approximately 0.7 grams per day (numbers based on 95% of all prescriptions from 2003 to 2014), which means an average monthly cost for patients of approximately $230 USD.

Drivers of Change in the International and National Attitudes in Cannabis

1. Scientific and clinical results and development;
2. Standardization of *Cannabis* products and administration forms on a

pharmaceutical level;
3. Education of key decision makers and healthcare professionals; and
4. Pressure of *Cannabis* patients (groups) through legislative efforts and court cases.

Summary

For the first time since its re-introduction into Western medicine during the 19th century, the evaluation of *Cannabis* for its therapeutic use is being explored in earnest. Many previously held beliefs about *Cannabis* and the cannabinoids simply do not hold up to scientific scrutiny. Modern scientific and objective evidence provides a firm foundation of new public policy, which clearly supports various types of *Cannabis* scheduling, descheduling, decriminalization, and regulation.

Many parties have developed monographs and regulatory guides for *Cannabis* and its derivatives. This includes but is not limited to medical *Cannabis* monographs published in the U.S., Canada, Czech Republic, and Holland. In Japan, three preparations concerning *Cannabis*-based medicines were listed in the Japanese Pharmacopoeia (1st edition, 1886; 4th edition, 1920; 6th edition, 1951). The European Union has also created agricultural standards for *Cannabis*[8,350,369,370]. The traditional use of *Cannabis* is recognized in formal pharmacopoeia's for indigenous ethnobotanical and spiritual uses.

As demonstrated in the comparison of drugs sections, the report by the UK Advisory Council reports that conclusions about the harmfulness of *Cannabis* abuse "lies somewhere between that of caffeine (an unregulated substance) and codeine[349]." Empirical scientific evidence demonstrates that standardized *Cannabis* products are an important treatment option with an acceptably reasonable safety margin.

Other Considerations - Quality Assurance of Medicinal Cannabis

Countries have Implemented Quality Assurance of Medicinal Cannabis and Related Products

The quality and safety of medical *Cannabis* and its derivatives are adequately addressed by existing national and local standards. The standards also address best practices for *Cannabis* operations, such as manufacturers, cultivation sites, laboratories, and dispensaries. Botanical medicines and herbal products are regulated; many of these botanical safety standards are directly applied to medical *Cannabis*. Several countries have made significant regulatory efforts to enact the existing national and local level standards for *Cannabis* production and distribution[8,103,349]. Some countries have published monographs (i.e., Czech Republic, Holland, U.S., and Canada) to specifically address the quality control of *Cannabis*, including methodology. Trade associations have published best practices for cultivation, dispensing, manufacturing and laboratory practices[371]. Furthermore, an abundance of national and international guidance documents provide quality control standards that address nearly every aspect of quality control and product safety for botanical substances, such as *Cannabis* and its derivatives.

One hurdle to quality control of medical *Cannabis* products is the present control status of *Cannabis* in countries such as the U.S. and also the controls under the conventions. National and international controls prevent adequate product testing in U.S. *Cannabis* programs and may inadvertently jeopardize public health. There has only been a single study, which examined the labeling accuracy (i.e., potency) of the *Cannabis* products' accessed through three state programs in the U.S. The study demonstrates that medical *Cannabis* product labels in the U.S. can be inaccurate [372]. However, the study also demonstrates that the current national controls for *Cannabis* impair the ability to address *Cannabis* product public health concerns. The DEA controls the release of analytical-quality standards for calibrating scientific instruments, which can only be purchased in necessary amounts if the operation has received a Schedule 1 license from the DEA. The DEA *will not grant* a Schedule 1 license to a state sponsored medical *Cannabis* laboratory, because the laboratory would receive medical *Cannabis* samples for analysis from *non*-DEA licensed sources (such as State licensed manufacturers, distribution centers, cultivation sites, patients, or doctors that recommend *Cannabis* to patients). Therefore, the Schedule 1 status of *Cannabis* blocks most laboratories from determining the precise potency of the product. It is difficult to address public health issues regarding medical *Cannabis* products while it remains in Schedule 1 status. However, testing for clinically relevant contaminants – such as heavy metals, bacteria, and fungus – can proceed without requiring DEA licensing but this product safety testing is also vulnerable to DEA or federal interference due to the scheduling status.

A normalizing factor for a medicine like *Cannabis* in the US could be for the United States Pharmacopeia (USP) to create a *Cannabis* monograph; these standards would be adopted to regulate *Cannabis* as a medicinal product nationally[373]. However, this action would grant pharmacists in the U.S. the ability to work with *Cannabis*, which is forbidden by the DEA. Hence, the USP *cannot* create a *Cannabis* monograph and still maintain compliance with the DEA.

Presently, the USP defers to the AHP monograph as the current standard for *Cannabis* products in the U.S. [368]. A recent meeting of the USP suggests drafting of the document will not begin until *Cannabis* is rescheduled to a status that recognizes its medicinal use and outstanding safety profile. The standards issued by the AHP monograph and American Herbal Products Association (AHPA) have been adopted by 16 U.S. states to regulate product safety for their medical *Cannabis* programs. Furthermore, AHPA, the trade association for the herbal products industry, has issued its medical marijuana manufacturing guidelines, completing its series of recommendations for state regulators in the areas of manufacturing, packaging and labeling, cultivation, dispensary operations, and laboratory practices.

Another example of production with good quality assurance/quality control is the Dutch program for medicinal *Cannabis*. This is produced under responsibility of the Ministry of Health and meets a number of quality requirements: consistent strength on THC and

composition of secondary cannabinoids, absence of microbiological contamination, pesticides and heavy metals, and humidity. Where there is a norm provided in the European Pharmacopoeia, this norm is followed[350].

The next sections briefly discuss published resources and guidance documents being used by governments to provide quality control and product safety around the world for agricultural products and botanical medicines, including *Cannabis*.

Good Agricultural and Collection Practices

The quality of raw material for botanical medicine can be safeguarded by using Good Agricultural and Collection Practices (GACP aka GAP) to the extent possible in all aspect of growing, harvesting, and storage[374]. Specific guidelines for regulators regarding *Cannabis* cultivation practices in the U.S. have been published by AHPA. These standards include requirements for standard operating procedure documentation, employee safety training, security, and batch tracking[371]. The American Herbal Pharmacopoeia has also released standards of quality control for *Cannabis* cultivation.

In The Netherlands, Czech Republic, and Italy, *Cannabis* to be used by patients, must be produced under GMP-like conditions. All products have to be fully tested (by an independent laboratory) per batch on cannabinoid content, absence of heavy metals, aflatoxins, pesticides (residue), and microbes to a level of <10 cfu. Standardization of *Cannabis* and *Cannabis* derivatives according to the monograph of herbal medicines of the European Medicine Agency (EMA) is mandatory and has to be proven for each batch.

In Austria (AGES) and the UK (GW Pharmaceuticals Ltd), *Cannabis* has to be produced under GAP; however, the derivatives from this *Cannabis* must be produced under GMP. Finished products need to be standardized according to regular [pharmaceutical] products.

Good Manufacturing Practice for Cannabis

Many guidance documents are available for reference and use in the manufacturing of plant medicines and products, any facility manufacturing products for human consumption should follow GMP. WHO has published guidelines on manufacturing botanical and herbal medicines, and the U.S. FDA has published guidance documents as well [375-378]. The AHPA manufacturing guidelines have a specific procedure for the recall of medical *Cannabis* products that do not meet "appropriate standards of identity, purity, strength, and composition and their freedom from contamination or adulteration." The AHP *Cannabis* monograph also sets limits for residues such as solvents and pesticides, heavy metals, bacteria, and fungi[8].

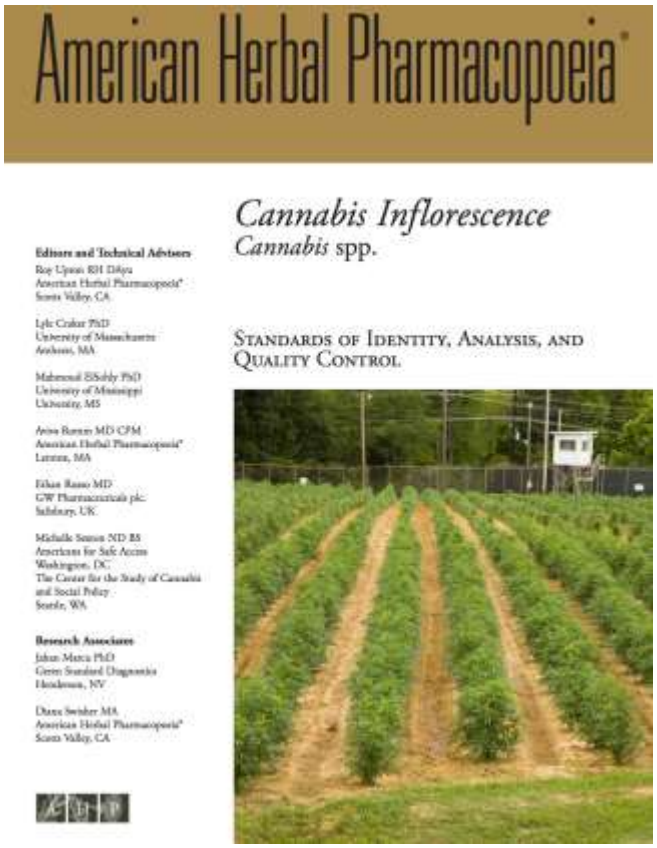

Figure 1. The front cover of the American Herbal Pharmacopoeia Cannabis Monograph (2014). This document has set the standard for cannabis quality control in several U.S. states.

Good Laboratory Practices

Methods used to determine potency should be scientifically validated by laboratories for several criteria including but not limited to specificity, linearity, accuracy, precision, and ruggedness. The FDA and other organizations (i.e., AHPA, USP, and AHP) have provided guidance documents that represent the current thinking on method validation and other aspects of good laboratory practices. There are also international standards for analyzing medical *Cannabis* products, which have been issued, for example, by the UN's Office of Drugs and Crime in their document entitled "Recommended Methods for the Identification and Analysis of *Cannabis* and *Cannabis* products"[379].

Below are a few examples of applicable guidance from a regulatory perspective, for analytical method validation for new methods, or methods not outlined in existing international and national regulatory documents:

- USP–NF, Validation of Compendial Methods; USP pharmacopeia 35, United States Pharmacopeia Convention, Inc., Rockville, MD. May 1, 2012 – December 1, 2012.
- U.S. FDA, Center for Drug Evaluation and Research (CDER), Reviewer Guidance on Validation of Chromatographic Methods, November 1994.
- American Herbal Pharmacopoeia *Cannabis Inflorescence*. Standards of Identity, Analysis, and Quality Control (2013).

Summary

Quality control and quality standards for medicinal *Cannabis* have been developed and adopted by several U.S. states, and many countries such as Canada, Israel, the Netherlands, and the Czech Republic to name a few. The current standards are presently being appropriately applied or implemented through third party licensed certification bodies, for regulating *Cannabis* and *Cannabis*-related products for human consumption.

The adopted product safety standards require *Cannabis* operations to implement quality control/quality assurance programs, batch tracking, adverse event tracking, employee safety training, and documentation of all relevant operational procedures, among several other criteria. The AHP and AHPA documents point to Patient Focused Certification (PFC) for implementation of these standards. PFC has offices in Washington, DC and the Czech Republic. PFC is the only international program that can verify that a country, region or state's *Cannabis* standards are being followed (www.patientfocusedcertification.com). PFC conducts a physical (site or facility) and documentation audit of the operation to generate an audit report that is submitted to a review board. PFC's review board features experts that have served in regulatory and scientific roles in U.S. presidential administrations, at the U.S. Department of Agriculture, in quality control laboratories, and related disciplines. PFC audited its first *Cannabis* operations in the U.S. in 2013 and in Europe in 2015, and is now an option for regulators in every country, state, or region with medical *Cannabis* access programs.

A successful public health outcome of product safety regulations has been demonstrated through successful product recalls in Canada and US. This required the cooperation of government, manufacturers, and 3rd party certifying bodies that resulted in consumer protection[380-386].

The largest hurdle to addressing public health concerns regarding the increasing availability of medical *Cannabis* products is the scheduling status of *Cannabis*. *Cannabis* needs to be thoughtfully and deliberately rescheduled, in order for producers, cultivators, manufacturers, laboratories, clinicians, researchers, and regulators to fully implement quality control standards for medical *Cannabis* products.

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