Update of Cannabis and its medical use

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Preface

This update of cannabis and its medical use was commissioned by the Secretariat of the Expert Committee on Drug Dependence, Department of Essential Medicines and Health Products, World Health Organization. This document is not a comprehensive review of the literature on cannabis, but a summary of the current status of the field and a framework to incorporate new information as it arises.

Terminology

Cannabis. Cannabis is the preferred designation of the plant *Cannabis sativa*, *Cannabis indica,* and of minor significance, *Cannabis ruderalis*.[1] According to the 1961 United Nations Single Convention on Narcotic Drugs, cannabis is defined as "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] Cannabis resin means "separated resin, whether crude or purified, obtained from the cannabis plant" . These definitions are narrower than the botanical definition and as a consequence, certain parts of the plant are not under international control. The term cannabis will be used instead of *marijuana,* or other names indigenous to local cultures, unless there is a need to refer to a specific phrase, e.g. *medical marijuana ballot initiatives*. Its use for medicinal, ritual or recreational purposes results from the actions of cannabinoids in the cannabis plant. These compounds also produce the unintended adverse consequences of cannabis.

Cannabinoids. Cannabinoids are basically derived from three sources: (a) *Phytocannabinoids* are cannabinoid compounds produced by plants *Cannabis sativa* or *Cannabis indica*; (b) *Endocannabinoids* are neurotransmitters produced in the brain or in peripheral tissues, and act on cannabinoid receptors; (c) *Synthetic cannabinoids,* synthesized in the laboratory, are structurally analogous to phytocannabinoids or endocannabinoids and act by similar biological mechanisms.

The focus on Cannabis

The evidence presented on potential medical uses and risks of cannabis in humans focuses on unprocessed, botanical cannabis and not isolated cannabinoids, some of which are medically approved. This is because it has been suggested that the cannabis plant contains chemicals that may be useful for treating illnesses or symptoms. Therefore, it has been advanced that whole plant cannabis could be used for medical purposes. The plant contains at least 750 chemicals, among which are some 104 different cannabinoids.[3,4] The boundaries drawn in this summary between cannabis and isolated cannabinoids is based on the following considerations:

(a) To avoid confusing terminology;
(b) The composition, bioavailability, pharmacokinetics and pharmacodynamics of botanical cannabis differs from extracts or purified individual cannabinoids;
(c) The bioavailability of active cannabinoids in cannabis, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), cannot be predicted because differences in smoking or vapor inhalation vary between users and types of delivery systems. In contrast, a fixed oral dose of a cannabinoid can be quantified in plasma or whole blood samples, yielding relatively predictable results;
(d) To avoid extrapolating to cannabis conclusions drawn from meta-analyses and primary sources reporting efficacy of purified and medically approved cannabinoid formulations at fixed doses, from randomized controlled trials (RCT). Approved cannabinoids are oral or sublingual spray preparations, whereas cannabis is used predominantly by smoking, inhalation from water pipes or vaporizing, a rapid

form of brain delivery considered a route of administration with higher addiction potential for some drugs, although this principle is not established for cannabis[5, 6, 7,8] (see Pharmacokinetics, below);
(e) To avoid extrapolation and appropriation of safety data generated from isolated and medically approved cannabinoids (with known doses) to whole plant cannabis, for which there are no guidelines for doses.

A description of cannabinoids that have undergone rigorous approval processes as legitimate medications (with reproducible composition of matter, purity and stability, fixed doses and known pharmacokinetic properties, dose-response efficacy, safety testing, side effect profiles, other criteria), is beyond the scope of this summary. At times, information on specific cannabinoids may be included, if comparisons with botanical cannabis are instructive.

Some cannabinoids have approved therapeutic applications. For instance, the psychoactive cannabinoid, THC (e.g., within Marinol®), has approval for either its anti-emetic and appetite stimulating properties or as a treatment for multiple scelerosis in Canada, Denmark and the United States, and Sativex®, a combination of THC and CBD, has approval for spasticity in 25 countries. Preclinical research has suggested other potential therapeutic applications for non-psychoactive phytocannabinoids. For example, CBD has putative therapeutic applications for treating psychosis, affective and seizure disorders, inflammation, and neurodegenerative disease.[9, 10, 11] Delta-9-tetrahydrocannabivarin, another phytocannabinoid, may also be useful for treating epilepsy and obesity.

Botanical cannabis is legally permitted for limited medical use in several countries including 23 states of the United States, in several European countries, Canada and Israel. Approval of cannabis to treat qualifying conditions has typically been based upon small RCTs, surveys, self-reports, *in vitro* or *in vivo* preclinical studies, testimonials or anecdotes delivered, ballot or legislative initiatives, and by advocacy groups.

Section 1. The cannabis plant and history of medical use

An overview by Kalant,[12] provides a historical context and an impression of *déjà vu*, as the medical benefits of cannabis continue to be debated globally. Cannabis grows profusely in most regions of the world, and has been used for millennia to produce fiber and rope. In the early 19th century, Europe was among the last civilizations to encounter the plant, with diverging reasons for using cannabis. In France, the psychoactive effects of cannabis were pursued, whereas in England the use of cannabis focused on medical purposes.[13] Cannabis extracts were listed in the British, and later in the US Pharmacopeia (1850), for sedative and anticonvulsant effects. Within a century, the British and then the US Pharmacopeia removed cannabis listings (1932, 1941, respectively). This was a result of the variable composition of plant preparations, short shelf-life, unpredictable doses, along with becoming overshadowed by newer, more targeted, effective pure drugs prescribed at known and reliable doses.[5] Subsequently, the risks of abuse, intoxication, and other negative consequences of cannabis consumption led to restrictive laws prohibiting the growth, possession and consumption of cannabis.

The movement to revive cannabis as a medicine is driven by multiple factors, many beyond the domain of science.[14] One propellant of the movement is the inadequate relief of current approaches for individuals harboring a number of debilitating chronic diseases or symptoms, including Multiple Sclerosis, Crohn's disease, Alzheimer's disease, cancer, and chronic pain. These and other medical conditions are frequently cited by proponents of cannabis for medical use.

Unresolved and critical questions persist: Is cannabis a safe and effective medicine for one or all of these conditions? For all people of all ages? For chronic use? For medical conditions characterized by cognitive impairment? Before addressing these central questions, it is essential to discuss cannabinoid chemistry and to survey endocannabinoid biology and function, as it is the foundation of claims for cannabis use in numerous medical conditions.

Section 2. Cannabis chemistry, preparations

2.1 Known chemistry of *Cannabis sativa*

The principal cannabinoids in the cannabis plant include THC, CBD, and cannabinol (CBN). THC is the primary psychoactive compound, with CBD, a non-psychoactive compound, ranking second. Generally, THC is found at higher concentrations than CBD, unless the ratio is deliberately altered. The known chemical composition of *Cannabis sativa* is constantly changing. New non-cannabinoid and cannabinoid constituents in the plant are discovered frequently. From 2005 to present, the number of cannabinoids identified in the whole plant increased from 70 to 104, and other known compounds in the plant increased from ~400 to ~650.[3,15,16] THC levels are also shifting, as breeding of different strains are yielding plants and resins with dramatic increases in THC content over the past decade, from ~ 3% to 12-16% or higher (w/w or percent THC weight/per dry weight of cannabis) and differing in different countries.[17,18,19,20,21] In some cannabis preparations, THC levels have risen even more radically by using a concentrating process (butane hash oil) that yields levels approaching 80% THC.[22] In an unregulated environment, other factors such as soil quality, bacterial and fungal contamination, the use of herbicides, pesticides, insecticides, water, light, soil availability or quality, temperature, bacterial or viral contamination, animal waste, insects, toxic chemicals, active compounds, heavy metals, bear on cannabis quality.[23]

2.2 Dose and dose delivery via different routes (smoking, vaporizers, edibles)

Cannabis is consumed by various routes, with the most common route smoking,[24] followed by vaporization, and then by the oral route. Cannabis products may be taken by ingesting edibles, sublingual or rectal administration, via transdermal delivery, eye drops and aerosols. However, few studies have documented their pharmacokinetics.

Inhalation by smoking or vaporization releases maximal levels of THC into blood within minutes, peaking at 15-30 minutes, and decreasing within 2-3 hours. Even with a fixed dose of THC in a cannabis cigarette, THC pharmacokinetics and effects vary as a function of the weight of a cannabis cigarette its preparation, the concentration of other cannabinoids, the rate of inhalation, depth and duration of puffs, volume inhaled, extent of breath-holding, vital capacity, escaped smoke and dose titration.[25,26] An extensive comparison of smoke (mainstream: smoke exhaled by a smoker and sidestream: smoke generated from the end of a cigarette) generated by igniting cannabis and tobacco cigarettes, showed marked qualitative similarities in specific compounds (e.g. ammonia, carbon monoxide, hydrogen cynanide, among others), and also significant quantitative differences.[27] The presence, in mainstream or sidestream smoke of cannabis cigarettes, of known carcinogens and other chemicals implicated in respiratory diseases is an important consideration when evaluating the safety and risks associated with cannabis smoking.[28] Lower temperature vaporization of cannabis has been postulated as safer than smoking, as it may deliver fewer high molecular weight components than smoked cannabis.[29] Increasingly, delivery of cannabis to the brain for medical or recreational use is via cannabis vaporization. Heating cannabis at moderate temperatures produces a fine mist of cannabis vapors that are inhaled via electronic cigarettes,[30,31] a delivery method that elicits a similar response while reducing exposure to pyrolytic byproducts. Vaporization reduces the characteristic odor of cannabis smoke, enabling diminished awareness by others

Hashish is a compacted resin of the plant, usually ingested or smoked. Hashish oil, a solvent-extracted liquid, is consumed by smoking or inhalation vaporization or as a food additive.[32] Users report more addictive behaviors and withdrawal symptoms with the high THC levels in this preparation. Oral ingestion from edibles is a slow absorption process and varies with the ingested matrix, as bioavailability is low (10-20%). Nevertheless, this does not result in a loss of pharmacological activity, because the major first-pass metabolite, 11-OH-THC, is also psychoactive. Oral ingestion delays the psychoactive effects to 30-90 minutes, with peaks at 2-3 hours and effects lasting for longer periods of time (4-12 hours), depending on THC levels. [33]

Smoking multiple cannabis cigarettes or chronic long term use leads to higher maximal concentrations, longer duration in blood, and longer biological half-life, compared with smoking a single cigarette or infrequent smoking. Chronic, frequent cannabis smokers' exhibit extended detection windows for plasma cannabinoids, reflecting a large cannabinoid body burden. Lipophilicity of THC accounts for its accumulation after chronic repeated use.[34,35,36,37,38] Metabolic elimination of THC from newly smoked cannabis is much slower after years of heavy cannabis use. When a single 6.8% THC cannabis cigarette was administered to frequent and to occasional users, plasma THC concentrations were significantly higher in frequent smokers than in occasional smokers at most time points from 0.5 to 30 h. Median (range) time of last detection was 3.5 h (1.1 to .30 h) in frequent smokers and 1.0 h (0-2.1 h) in occasional smokers. In chronic heavy (daily) cannabis users, THC can be detected in blood during a month of sustained abstinence. These findings are consistent with THC lipophilicity and time course of persisting neurocognitive impairment reported in recent studies.[39,40]

Section 3. Cannabinoid biology, signaling in brain and peripheral tissues

From an evolutionary perspective the cannabinoid signaling system is ancient, and is found in invertebrates and advanced vertebrate organisms. [41 , 42] The endocannabinoid system has four main components:
(1) G protein-coupled cannabinoid CB1 and CB2 receptors
(2) Endogenous endocannabinoids that target these receptors, and possibly other receptors
(3) Enzymes that catalyze endocannabinoid biosynthesis and metabolism
(4) Mechanisms involved in cell accumulation of specific endocannabinoids

3.1 Cannabinoid receptors: distribution, regulation, function

The CB1 receptor is expressed in the brain and peripheral tissues. In both locales, it has multiple functions.[43] In the brain, it is the most abundant of the G-protein coupled receptors, and mediates most, if not all the psychoactive effects of THC in cannabis. Its distribution is consistent with the pharmacology of cannabis: CB1 receptors are enriched in the cerebellum (cognition, coordination), hippocampus (learning and memory), cortex (cognitive function, executive function and control, integration of sensory input), basal ganglia (motor control, planning) ventral striatum (prediction and feeling of reward), amygdala (anxiety, emotion, fear), hypothalamus (appetite, hormone levels, sexual behavior), brain stem and spinal cord (vomiting, pain).[44,45,46,47]

CB2 receptors are predominant in the periphery, on immune cells, hematopoietic systems and other locales. There is evidence of CB2 receptor expression in brain.[55,56,48] In the brain, CB2 receptors also modulate the release of chemical signals primarily engaged in immune system functions (e.g. cytokines). CB2 receptors are of considerable interest because all the psychoactive effects of THC in humans can be abolished by selective antagonism of the CB1 receptor, implying that THC activation of CB2 does not produce psychoactive effects.[49] Accordingly, CB2 receptors are a promising target for therapeutics as they may circumvent the adverse effects promulgated by cannabis or THC that engender psychoactive effects via CB1 receptors.

3.2 Endocannabinoids and signaling

Endocannabinoids play a fundamental role in regulating pleasure, memory, thinking, concentration, body movement, awareness of time, appetite, pain, and sensory processing (taste, touch, smell, hearing, and sight), and brain development.[56,57] Endocannabinoids acting at CB1 receptors (and possibly CB2 receptors) modulate and "fine-tune" signaling in most brain regions, to enable the brain to adapt to signals generated by multiple sources.

3.3 Function of the endocannabinoid system in the brain

Understanding the multiple functions of endocannabinoid signaling in the brain offers insight into the pharmacological effects of cannabis and other exogenous cannabinoids, their therapeutic potential and undesirable adverse effects. An overview by Kalant[50] describes in depth "on demand" endocannabinoid modulation of excitatory and inhibitory synaptic transmission and regulatory functions in the brain.[51]

3.3.1 ***Brain development, neurogenesis, psychiatric disorders:*** Endocannabinoid signaling is crucial for brain development, and guides neural stem cell survival and proliferation, cell fate decisions and the motility and differentiation of ensuing neuronal and glial cells.[52] Developmental endocannabinoid signaling, from fetus to young adult, may be susceptible to cannabis use during pregnancy and adolescence, possibly affecting brain structure and function. Endocannabinoids and cannabis-altered endocannabinoid signaling may contribute to neuropsychiatric diseases that are of developmental origins and in which modifications to signaling have been observed: autism,[53] schizophrenia,[54] bipolar disorder[55] and depression.[56] The central role of the cannabinoid system in promoting adult neurogenesis in the hippocampus and the lateral ventricles provides insight into the processes underlying post-developmental neurogenesis in the mammalian brain. Both THC[57] and CBD[58] inhibit neurogenesis in adolescent or adult rodent brain, a process of potential relevance to a wide range of cannabis-induced adverse events.[59]

3.3.2 ***Neuroprotection:*** Cannabinoids and CB1, CB2 receptors display neuroprotective effects in the brain by preventing or decreasing the severity of damage resulting from mechanical, blood flow, or other forms of injury. Genetic ablation of the CB1 receptor exacerbates ischemic stroke,[60] with CB2 agonists providing anti-inflammatory properties and CB1 activation promoting hypothermia. The use of cannabis for this purpose is compromised by psychoactive effects and the development of tolerance to its neuroprotective effects.

3.3.3 ***Cannabinoids and sensory function (olfaction, auditory, pain):*** The endocannabinoid system contributes to olfactory, auditory and pain sensations. A review of these functions is beyond the scope of this summary but readers are referred to an excellent overview.[61] There is extensive anatomical overlap of the opioid and cannabinoid receptor systems, and it appears probable that functional interactions between them occur in the production of analgesia.

3.3.4 ***Appetite and nausea:*** A number of nuclei in the medulla are involved in the regulation of appetite and nausea. These nuclei coordinate sensory input from the brainstem, vagal complex, vestibular organs, and peripheral organs. Endocannabinoids and CB1 agonists inhibit vagal fibers to promote eating and CB1 antagonists to decrease or inhibit food intake.[62]

3.3.5 ***Sleep:*** Endogenous and exogenous cannabinoids, including cannabis and THC, affect sleep patterns.[63] There is poor quality evidence that cannabis or cannabinoids have therapeutic benefit in sleep disorders.[64]

3.3.6 ***Affective disorders:*** The endocannabinoid system has mood elevating, anti-depressant and anxiolytic effects. The anxiolytic response to cannabis is biphasic, implying that cannabis dosing is a

critical factor in minimizing risk of anxiety, depression and maximizing benefit.[65,66,67] Cannabis at high doses increases the risk for depression or anxiety possibly by down-regulating CB1 receptors.[68,69,70,71]

3.3.7 ***Seizure activity:*** The endogenous cannabinoid system inhibits seizure susceptibility. Therefore it is unsurprising that exogenous cannabis has antiseizure activity. However, if THC levels are high or cannabis is consumed by susceptible individuals, THC may promote seizures.[72] CBD has therapeutic potential as antiepileptic drug without the psychoactive effects, or potential for pro-seizure activity of whole plant cannabis.[73,74]

3.3.8 ***Motor function:*** The endocannabinoid system plays a complex role in regulating motor pathways, which conceivably are relevant to symptomatic relief, or to addressing the underlying pathology in a wide range of neurological diseases characterized by motor impairment.[75] CB1 receptors are abundant in brain regions that regulate motor function and coordination, including the basal ganglia, cerebellum. CB1 receptors are down-regulated in several neurological conditions.[76]

3.3.9 ***Cognitive functions:*** Cannabinoids can both facilitate and degrade learning processes dependent upon the process involved. Endocannabinoids apparently facilitate various forms of learning and memory processes in a number of brain regions. The endogenous cannabinoid system is also implicated in extinguishing learning of aversive situations. On the other hand, THC and cannabis decrease working memory, apparently by actions in the hippocampus, a brain region critical for learning and memory. The memory decrements induced by THC or cannabis resemble hippocampal lesions. These impairments may result from suppression of glutamate release in the hippocampus, which is responsible for the establishment of synaptic plasticity.[77,78,79]

3.4 Function of the endocannabinoid system in peripheral tissues

Endocannabinoid signaling systems are found nearly ubiquitously in the peripheral tissues, with their distribution possibly accounting for the myriad of effects and potential medical applications of cannabinoids. This summary is based on a recent review.[80]

3.4.1 ***Gastrointestinal (GI) tract:*** CB1 and CB2 receptors are highly expressed on enteric nerves and on enteroendocrine cells (CB2) throughout the intestinal mucosa, on immune cells (CB1 and CB2), and enterocytes (CB1 and CB2). Many gut functions are regulated by endocannabinoids critical for central nervous system (CNS) control of its metabolic and homeostatic functions.

3.4.2 ***Cardiovascular system:*** CB1, CB2, endocannabinoids and their enzymes are present in cardiovascular tissues and may contribute to the development of common cardiovascular disorders. An acute action of cannabis is mild tachycardia, with increases in cardiac output and increased myocardial oxygen requirement.

3.4.3 ***Liver:*** Cannabinoid receptor expression is normally low in liver, with CB1 and CB2 receptors acting in opposite directions: CB2 receptors mediate several biological functions in various types of liver cells, and CB1 blockade contributes to beneficial metabolic effects. CB1 expression increases in pathological states, promoting fibrogenesis, steatosis, and cardiovascular complications of liver disease. In contrast, CB2 is protective, reducing these indices of liver dysfunction.

3.4.4 ***Immune System:*** Endocannabinoids modulate the functional activities of immune cells, largely though CB2 receptors, providing novel targets for therapeutic manipulation.[81]

3.4.5 ***Muscle:*** Endocannabinoid signaling (largely through CB2 receptors) contributes to regulating energy metabolism in muscle and the formation of new muscle fibers.

3.4.6 ***Reproductive System:*** Endocannabinoid signaling, primarily mediated by the CB2 receptor regulates all critical stages of pregnancy and affects pregnancy events. Signaling is also involved in the preservation of normal sperm function, and thus male fertility.

3.4.7 ***Skin:*** Endocannabinoid signaling, through both CB1 and CB2, is involved in regulating skin functions such as proliferation, differentiation, cell survival, immune responses and suppressing cutaneous inflammation. Exogenous modulators of the receptors could clarify the role of the endocannabinoid system in hyperproliferative skin conditions, allergic and inflammatory skin diseases.

3.4.8 ***Other organs:*** The role of endocannabinoid signaling in respiratory tract and urinary system remains unclear, but there is preliminary evidence that CB1 and CB2 receptors may contribute to kidney disease.

Section 4. Cannabis toxicity in humans

The primary risks of cannabis consumption have been discovered by investigating users of cannabis for recreational purposes. Few studies have reported on long term consequences of cannabis if used for medical purposes. Cannabis engenders acute pharmacological effects, longer term health risks for the brain, body and behavior, and public safety concerns.

4.1 Cannabis and the central nervous system (CNS)

4.1.1 ***Cognition and coordination***.
Crean et al. (2011) reviewed a broad spectrum of cognitive functions designated as executive functions[82] and identified studies that reported that attention, concentration, decision-making, impulsivity, inhibition (self-control of responses), reaction time, risk taking, verbal fluency and working memory were impaired acutely in a dose-dependent manner, although these effects were not consistently observed.

Acutely, cannabis impairs several components of cognitive function, with the most robust effects on short-term episodic and working memory, planning and decision-making, response speed, accuracy and latency.[83] Some studies also report increased risk-taking and impulsivity.[84] Less experienced cannabis users undergo stronger intoxicating effects on attention and concentration than those with established drug tolerance. Acutely, cannabis also impairs motor coordination, interferes with driving skills and increases the risk of injuries. Evidence suggests recent smoking is associated with substantial driving impairment, particularly in occasional smokers,[85] with implications for work in safety-sensitive positions or operating a means of transportation, including airplanes. Complex human/machine performance can be impaired as long as 24 h after smoking a moderate dose of cannabis and the user may be unaware of the drug's influence.[86]

Recently abstinent cannabis users (7 hours to 20 days) may experience impairment in attention, concentration, inhibition and impulsivity during the period in which THC and its metabolites are eliminated.[87] The greatest residual deficits in executive function are found following prolonged use of cannabis. In real world situations, in the context of work and everyday life, cannabis use is associated with impaired cognitive function, mood, lower alertness, and slower response. Users also experienced working memory problems at the start, and psychomotor slowing and poorer episodic recall at the end of the working week, possibly 'hangover'-type effect which may increase with frequency of use. The results demonstrate the importance of testing within the context and routine of everyday life.[88]

Cannabinoids persist even after one month, and are detectable in blood of chronic daily cannabis smokers during sustained abstinence.[89] Cannabis continues to impair executive functions, with the chronic, heavy

cannabis users showing the most enduring deficits. Decision-making, planning, concept forming are the most prominent and durable deficits, but verbal fluency (information retrieval from memory) may or may not persist at this point.

4.1.2 ***Imaging techniques*****:** A window into the brain of cannabis users can be accessed by various techniques that can assess measurement (MRI), neurochemistry (PET imaging), connectedness or "connectome" (diffusion tensor imaging), function (fMRI), and metabolism (MRI spectroscopy). A number of studies have shown differences in the brains of heavy cannabis users and non-users.[90] Further descriptions of brain changes are provided in the Section 4.3.2. *Adolescence*. Intriguingly, a recent study concludes that cannabis use conceivably is attributable to pre-existing, predispositional differences in the brains of users compared with non-users.[91]

4.1.3 ***Psychosis and Schizophrenia:*** The strong association between cannabis use and psychosis or schizophrenia has been recognized for over two decades, in at least four ways: (1) cannabis produces a full range of transient schizophrenia-like positive, negative, and cognitive symptoms in some healthy individuals. The induction of psychosis by cannabis was originally reviewed by Warnock in 1903[92] and substantiated subsequently;[93,94] (2) in those harboring a psychotic disorder, cannabis may exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness;[95] (3) susceptible individuals in the general population develop a psychotic illness with heavy cannabis use, which is associated with age of onset of use, strength of THC in cannabis, frequency of use and duration of use;[96,97] (4) cannabis use is associated with lowering the age of onset of schizophrenia.[98] It is likely that cannabis exposure is a "component cause" that interacts with other factors to precipitate schizophrenia or a psychotic disorder, but is neither necessary nor sufficient to do so alone.[99] Symptoms of schizophrenia increase with cannabis use and strength. The magnitude of the symptoms is associated with amount used and frequency of use. In individuals with an established psychotic disorder, cannabis can exacerbate symptoms, trigger relapse of the disorder, and have negative consequences on the course of the illness.[100,101]

4.2 Harmful effects of cannabis in peripheral tissues

An overview of the harmful effects of cannabis was recently published, and forms the basis of some comments below.[102]

4.2.1 ***Pulmonary disease and lung cancer:*** After adjusting for tobacco use, chronic cannabis use is associated with an increased prevalence of symptoms of chronic bronchitis, and is compatible with injury and inflammation involving the central airways,[103] based on widespread endoscopic and microscopic evidence of injury and inflammation involving the central airways of habitual smokers of cannabis. These include loss of ciliated epithelium and replacement by mucus-secreting goblet cells, the frequency and severity of which were comparable to that of smokers of tobacco alone.[104, 105] What is less clear is the impact of chronic cannabis use on lung function. In the past, as cannabis has been consumed less frequently and as current daily users in the United States among college age students is at its highest levels in three decades),[106] a recent longitudinal study of occasional and low cumulative cannabis users may not be relevant to current patterns of daily use. This study found that cannabis use was not associated with adverse effects on pulmonary function.[107] Cannabis smoke does not appear to contribute to chronic obstructive pulmonary disease nor are its carcinogenic effects clear at the present time. Low levels of cannabis exposure do not appear problematic but regular cannabis smokers are more likely to harbor chronic bronchitis and increased rates of respiratory infections and pneumonia.[108]

4.2.2 ***Vascular conditions:*** Cannabis use is also associated with vascular conditions that increase the risks of myocardial infarction, stroke, and transient ischemic attacks during cannabis intoxication.[109]

4.2.3 ***Cannabis and carcinogenic potential:*** One concern of the use of cannabinoids, particularly inhaled cannabis, is carcinogenic potential. There is currently no consensus on whether cannabis use is associated with overall cancer risk. This section summarizes systematic reviews of the literature.[110,111,112,113] Cannabis smoke is carcinogenic in rodents and mutagenic in the Ames test (a cancer test performed for candidate medications in rodents, before drug testing in humans). Cannabis smoke contains several of the same carcinogens as tobacco smoke, at up to 50% higher concentrations and with three times the tar per cigarette. Respiratory mucosa exposed to chronic cannabis smoke shows pre-neoplastic histological and molecular changes. Despite this *in vitro* and *in vivo* evidence, there is no strong correlation between cannabis use and the development of human cancers. For example the link between head and neck squamous cell carcinoma (HNSCC) risk and cannabis is inconsistent. Three studies have found a statistically significant 2.6-fold increased risk of HNSCC in cannabis users compared with controls when adjusted for cannabis dose, duration of use, and confounding variables such as alcohol or tobacco use. Similarly, heavy cannabis smokers in Northern Africa had a 2.62 increased risk for nasopharyngeal carcinomas. At this point the majority of studies do not support conclusions that smoked cannabis is strongly associated with an increased risk of head and neck cancers, once tobacco and alcohol intake are controlled.[114]

A recent review of 34 epidemiologic studies on upper aerodigestive tract cancers, lung cancer, testicular cancer, childhood cancers, all cancers, anal cancer, penile cancer, non-Hodgkin lymphoma, malignant primary gliomas, bladder cancer, and Kaposi sarcoma studies did not appear to support an association of lung cancer with cannabis use, possibly because of the smaller amounts of cannabis regularly smoked compared with tobacco. For other cancer sites, there is still insufficient data to make any conclusions. As cannabis use rates may change, well-designed studies on the association between cannabis use and cancer will be warranted.[115]

However, a pooled analysis of three studies of active male cannabis smokers in North Africa found that the risk for developing lung cancer was increased 2.4 times, but this heightened risk could be confounded by tobacco smoking.[116] A case controlled study of patients with lung cancer under 55 years of age in New Zealand found an 8% increased risk for each joint-year (one joint/day/year) of cannabis use. This effect persisted only in the highest tertile of cannabis use (>10.5 joint-years of exposure) when adjusted for tobacco use.[117]

With cannabis use, there is a trend towards increased non-seminoma testicular germ cell tumors, especially among those who smoke cannabis at least weekly,[118] prostate cancer (3-fold risk), and cervical cancer (1.4 fold risk). The incidence of oropharyngeal and oral tongue cancers has increased over the last 20 years. In a pooled analysis of nine case-control studies from the United States and Latin America, ever cannabis smokers had an elevated risk of oropharyngeal and a reduced risk of oral tongue cancer. The risk of oropharyngeal cancer remained elevated among never tobacco and alcohol users. The risk of oral tongue cancer was reduced among never users of tobacco and alcohol. These results suggest that the association of cannabis use with head and neck carcinoma may differ by tumor site, with both possible pro- and anticarcinogenic effects of cannabinoids. Additional work is needed to rule out various sources of bias, confounds and misclassification of cannabis exposure.[119]

A US study of health maintenance organization members found an increased risk of malignant primary gliomas in people who smoked cannabis once per month or more, but found no dose-response relationship.[120] Smaller studies have implicated cannabis use in the development of bladder cancer and testicular germ cell tumors. The reasons for the great heterogeneity in epidemiologic studies correlating cannabis use and cancer may be related to difficulties in quantifying cannabis use, unmeasured confounders in the cases or controls, and variable expression of cannabinoid receptors in target tissues. Overall, smoked cannabis is associated with a slightly elevated risk for certain cancers.

4.2.3 ***Fertility*****:** *In vivo* and *in vitro* studies have shown that cannabis may disrupt the hypothalamus-pituitary-gonadal axis, spermatogenesis, and sperm function (motility, capacitation, acrosome reaction).[121]

4.2.4 ***Cannabis hyperemesis syndrome*****:** Cannabis has antiemetic properties, one indication for its use medicinally. However, a number of cases of cannabis-induced hyperemesis have been reported. This is a paradoxical clinical syndrome of the gastrointestinal tract and brain which has been designated the title 'Cannabis Hyperemesis Syndrome'. Patients exhibit a triad of symptoms: cyclic vomiting, chronic cannabis use, and compulsive hot water bathing, attributable to heavy cannabis use.[122,123]

4.2.5 ***Cannabis, emergency department mentions, mortality*****:** As cannabis use rises, emergency department mentions from 2004-2011, for cannabis alone or in combination with other drugs, increased substantially. As examples, it represents 36% of all illicit drug mentions in the U.S and 31% in an urban emergency department in Switzerland.[124,125] In a consortium of 16 sentinel centers across Europe reporting acute drug toxicity presentations in emergency departments, cannabis ranked third among drugs after heroin and cocaine.[126] It has also been reported that cannabis is a small, but increasing burden on emergency services in Australia.[127] The mortality of patients with a cannabis use disorder is also of concern.[128]

4.3 Cannabis during development: the adolescent and prenatal periods

4.3.1 ***Fetus:*** It is challenging to fully clarify the role of cannabis in fetal development, given the range of potentially confounding variables associated with cannabis use during pregnancy (tobacco, alcohol, nutrition, psychology). Nevertheless, accumulating evidence suggests that prenatal exposure may interfere with normal development and maturation of the brain. Children exposed to cannabis *in utero* demonstrate impaired attention, learning and memory, impulsivity and behavioral problems and higher likelihood of using cannabis when they mature.[129,130,131,132,133,134,135] Human research in this domain is still limited, and contrasts with nicotine or alcohol research.

4.3.2 ***Adolescence***

- *Vulnerability of the developing brain*

Accumulating evidence reveals that regular, heavy cannabis use during adolescence is associated with more severe and persistent negative outcomes than use during adulthood. The adolescent brain may be more vulnerable to cannabis than adults, and early initiation of heavy use may disrupt the trajectory of normal brain development. Heavy or regular adolescent cannabis users manifest a range of cognitive deficits, including impairments in attention, learning, memory, and response perseveration. These deficits are similar in adults but in adolescents, they are more likely to persist and may only recover after longer periods of abstinence.[136] Earlier onset users show greater impairment in cognitive domains, including learning and memory, attention and other executive functions.[137,138] Decrements in cognitive function are correlated with initiation of cannabis use during adolescence.[139]

A recent large-scale longitudinal study followed a large cohort from childhood to age 38, and assessed neuropsychological functioning at multiple time points. It revealed that adolescents who used cannabis weekly or harbored a Cannabis Use Disorder (CUD) before the age of 18, showed larger neuropsychological decline, and I.Q. reduction than those who became dependent during adulthood. The results are consistent with cross-sectional findings in adult populations, and reinforce the conclusion that sustained abstinence may not enable cognitive functional recovery, if use was initiated during adolescence. A subsequent re-analysis showed that socioeconomic differences did not account for the sustained loss of I.Q.[140,141]

Brain imaging has generally revealed changes in brains of adolescents or adults who initiated cannabis during adolescence.[142,143,144] Cannabis users have smaller whole brain and hippocampus, reduced cortical

grey matter and insular cortical thickness[145,146] that is associated with level of use. Some studies found correlations between brain changes and deficits in learning and memory.[147] Age of onset of cannabis use apparently is not as important in hippocampal shrinkage, compared with amount and frequency of use.[148] Changes in cortical volume may predate and predispose individuals to use cannabis, but not in hippocampus.[149] This region is vulnerable to heavy cannabis use, regardless of age.

- *Education and cognition*

The interaction between cannabis use and education is complex. In several countries, cannabis use is high among high school and college students (e.g. Australia, US, Canada). Because it impairs learning and memory during, and for days after use, with cumulative effects (see above), learning in a school environment may be compromised for a considerable period during the school year.[150] Cannabis use is associated with poor grades and with high drop-out rates,[151] with those dropping out of school engaging in high rates of frequent cannabis use.[152] Environmental and other risk factors add to the complexity of this association.[153] A longitudinal study showed that early initiation of heavy cannabis use is associated with lower income, lower college degree completion, greater need for economic assistance, unemployment, and use of other drugs.[154,155,156] Another longitudinal study, based on student self-reports, teacher ratings and high school dropout records, showed that cannabis is not an isolated or benign event in the life of adolescents but part of an overall problem behavior syndrome.[157]

- *Psychosis and Schizophrenia*

Research has shown an association of early age of onset of cannabis use to earlier onset of schizophrenia and higher prevalence of psychosis, including mania.[158, 159, 160, 40, 161, 162] The emergence of psychotic symptoms apparently is dose-dependent with more robust symptoms as use and frequency escalate. Some have questioned the association of cannabis use to adverse outcomes in adolescents, claiming either no effects, or environmental components as the underlying risk factor.[163,164]

- *Use of other drugs*

Surveys in France, the United States, Australia, have shown that the prevalence of a substance use disorder, for drugs other than cannabis, is higher in adolescents who initiate cannabis use, and as a function of age of initiation.[165,166,167] This pattern has been observed in controlled twin studies, in which one pair initiated cannabis use prior to the age of 17 and the other did not.[168,169]

- *Bone*

Endocannabinoid signaling regulates bone elongation and remodeling by modulating bone cell proliferation, communication between cells, and neuronal control of bone remodeling. In view of THC's profound effects on murine bone growth, this may be relevant to adolescents who consume cannabis during a rapid phase of growth.

4.4 Cannabis and society

Cannabis engenders many consequences to society, which are beyond the scope of this overview. Below is a summary of several adverse consequences.

4.4.1 ***Cannabis and driving.*** Cannabis impairs driving ability and confers a higher risk for motor vehicle accidents. In experimental settings, cannabis impairs psychomotor skills and cognitive functions associated with driving, including vigilance, time and distance perception, lane tracking, motor coordination, divided attention tasks, and reaction time.[170] Drivers may attempt to compensate by driving more slowly and increasing their following distance. On highways, cannabis is the most frequently reported illicit drug in connection with impaired driving and accidents, including fatal accidents. In the US, (2013), 62.6% of fatally injured drivers were tested for drugs and more than one-third (34.7%) were positive for cannabis.[171] In other countries some attribute increased roadside accidents to

cannabis.[172,173,174,175] The use of cannabis in combination with alcohol increases the risk of impairment more than use with either drug alone as the effects were additive.[176]

4.4.2 ***Cannabis, employment, the workplace*****.** The effects of cannabis use on cognition in the context of work and everyday life, or whether off-site cannabis use endangers a worker or his colleagues while at work, has not been systematically investigated. One study that examined association between cannabis use and cognitive performance, mood and human error at work found that cannabis use was associated with impairment in both cognitive function and mood, though cannabis users self-reported no more workplace errors than controls. Users also displayed lower alertness, slower response organization, working memory problems at the start, and psychomotor slowing and poorer episodic recall at the end of the working week. Subtle effects on cognitive function may be exacerbated with fatigue or work-related demands.[177] During an economic downturn, cannabis use was recently shown to increase unemployment among users.[178] Combined with alcohol, vaporized cannabis yields higher maximum concentrations of blood THC (than without alcohol) detected 8.3 hours later, possibly explaining why performance is more impaired if cannabis is combined with alcohol in this manner.[179,180,181]

There is ample evidence indicating that neurocognitive impairment from cannabis persists from hours to weeks. A return to a non-intoxicated state does not ensure a full return of neurocognitive function in the workplace.[182] In a summary of the dilemmas that cannabis for medical use has created for the workplace, it was pointed out that ensuring safety of workers who are under the influence or who recently consumed cannabis is not possible.[183]

4.4.3 ***Cannabis and advanced education.*** Several studies have shown that cannabis use can adversely affect academic achievement among adolescents. These are reviewed in Section 4. Cannabis use during college can be a barrier to academic achievement. A large longitudinal cohort study of college students showed that frequency of cannabis use was a significant factor in poor class attendance, lower grades, and longer time to graduate from college. [184,185] A significant proportion of cannabis-using college students meet diagnostic criteria for cannabis use disorder (CUD), and even in the absence of CUD disorder, users appear to be at risk for potentially serious cannabis-related problems. The prevalence of CUD among a sample of college students at one university was relatively high (9.4%), and was 24.6% among past-year cannabis users. Among the most prevalent cannabis-related problems, cannabis users reported concentration problems (40.1%), driving while high (18.6%), missing class (13.9%), and placing oneself at risk for physical injury (24.3%) even among those who did not endorse a CUD criteria. [186]

Section 5. Dependence, Abuse and Cannabis Use Disorder (CUD)

5.1 Current prevalence of use, scope, duration, significance of abuse.

Cannabis is the most widely used illicit substance in the world.[187] There is strong scientific support for concluding that cannabis has high potential for abuse, is actually abused and is addictive. Diagnostic guidelines by both The International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) have designated that cannabis is addictive, and currently recognize cannabis related dependence disorders.[188]

Psychological or physiological dependence**:** Neuroadaptation that leads to withdrawal is based on individual responses and also depends on the extent and frequency of use. As with all addictive drugs, addiction, habituation, and abuse to cannabis is characterized by psychological symptoms during the initial abstinent phase (irritability, anger or aggression, nervousness or anxiety, sleep difficulty or insomnia, decreased appetite, weight loss, restlessness, depressed mood), but is not necessarily accompanied by physiological or physical symptoms during withdrawal. However, abstinence in heavily

addicted cannabis users unmasks physical neuroadaptation, manifested by physical, significant discomfort which can include stomach pain, shakiness/tremors, sweating, fever chills, headache. The more pronounced the withdrawal, the more predictive the symptoms are of relapse.[189,190] The validity of cannabis withdrawal has been demonstrated in preclinical, clinical, and epidemiological studies. Cannabis withdrawal is reported by up to one-third of regular users in the general population and by 50-95% of heavy users in treatment or research studies.[191] The clinical significance of cannabis withdrawal is demonstrated by use of cannabis or other substances to relieve it, its association with difficulty quitting, sleeping, physical symptoms, increased violence among individual predisposed to violence, and worse treatment outcomes associated with greater withdrawal severity.[192,193,194,195,196]

***Globally*:** Approximately 13.1 million people are cannabis dependent globally.[197] Global statistics are accumulated by the United Nations Office on Drugs and Crime (UNODC),[198] which provide an insight into the trends of cannabis world-wide. Cannabis is the main drug causing treatment demand in Africa and in the United States.[199] Comparisons between countries are challenging because the reporting of cannabis use is not uniform among countries and is not conducted annually in each country. These comparative trends may be current or out-of date or age groups may differ by country. Examples of prevalence data from some countries are given below.

In Europe, rates of use, and prevalence of CUD vary by country, as documented by the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) for EU Member States.[200] It is estimated that cannabis has been used at least once (lifetime prevalence) by about 77 million Europeans that includes one in four of all individuals 15-64 years old. Considerable differences exist between European countries, with national prevalence figures varying from 1.6-32.5%. Among young adults (15-34 years), lifetime prevalence of cannabis use varies from 1-45.1 %, with a weighted European average of 32.2%. It is estimated that about 15.4 million (11.7%) young Europeans have used cannabis during the last year and 6.5% during the last month. In the 2011 surveys of the twenty-four Member States and Norway, lifetime cannabis use among 15-16 years ranged from 5% in Norway to 42% in the Czech Republic. A significant minority of cannabis users consume cannabis intensively. Daily or almost daily cannabis use is defined as use on 20 or more days in the month preceding survey. Data from 22 countries, suggest that around 1% of adults aged 15-64 years (~three million), report using the drug this frequently. Over two-thirds of frequent users are between 15 and 34 years, and in this range, over three-quarters are male.[201]

Data from the United States of America indicates that the prevalence of cannabis use increases when perceived risk of use decreases; perception of risk has declined in the face of a changing legal status of the drug, with consequent rise in daily use among youth.[202] The percent of high school and college students who are daily users is higher now than it has been for decades.[203] The prevalence of cannabis use disorder is approximately 9% of users overall (a percent calculated prior to currently high THC levels), 16% of early initiators and 25-50% of daily users.[204,205] The most recent study on prevalence of cannabis use disorder among users in the US reported 30.5% of past year users harboring a CUD.[206] This is greater than previous estimates and may reflect the consequences of high cannabis potency and more frequent daily use. Admissions for CUD have climbed significantly recently,[207] as have emergency department mentions. More youth are in treatment for the disorder than for an alcohol use disorder, and college age students manifest severe problems with cannabis use or CUD.[208,209,210]

Canadians are among the highest past-year users of cannabis. Based on data from the 2012 Canadian Community Health Survey-Mental Health, 42.5% of the population reported having ever used cannabis, and 12.2% reported use in the past year, with highest rates among 18- to 24-year-olds (33.3%). Use rates differed across the country, with past-year use higher in British Columbia and Nova Scotia and lower in Saskatchewan, compared with the rest of Canada. The percentage of males who had ever used cannabis rose from 47% to 49.4% whereas the prevalence of lifetime use among females was stable at 36%.[211] In

contrast with the United States, cannabis use may be down among teens and young adults a new report from Statistics Canada suggests. [212]

Among illicit use of drugs, cannabis had the highest rate of use, with the cohort of 20-29 year olds consuming the most. In 2013, it was estimated that about 6.6 million (or 35%) people aged 14 or older had used cannabis in their lifetime and about 1.9 million (or 10.2%) had used cannabis in the previous 12 months. About one in 20 Australians (5.3%) had used in the month prior to the survey and 3.5% had used in the previous week. Among people aged 14-24, the age at which they first tried cannabis increased between 2010 and 2013, cannabis users were more likely to try cannabis in their teens, and age of first use was younger compared to other illicit drugs. One-third (32%) of recent cannabis users used it as often as weekly, and older people (50 or older) were more likely than younger people to use cannabis regularly, with at least four in 10 recent users in these age groups using it as often as once a week or more. One-fifth (19.8%) of recent cannabis users stated that all or most of their friends currently used cannabis, in contrast to only 0.8% of those who had never used the drug. In parallel with the US, between 2010 and 2013 the proportion of people aged 50-59 and 60 or older using cannabis rose (from 5.5% to 7.3% and from 0.5% to 1.2%, respectively) and is at the highest levels seen over the past decade among these age groups, which may reflect an ageing cohort of cannabis users.[213]

Section 6. The use of cannabis for medical purposes

This section excludes individual therapeutic cannabinoids, extracts of cannabinoids approved by government agencies qualified to evaluate medicinal products, candidate cannabinoid therapeutics undergoing appraisal by an evidence-based drug approval process, individual cannabinoids of therapeutic potential assessed in preclinical research (i.e., *in vitro* or *in vivo* animal studies) or in pilot clinical studies, endocannabinoids and modulators of endocannabinoid synthesis, metabolism or trafficking. The rationale for exclusions is provided in the **Terminology** section. Essentially, it is based on a need to separate current evidence for the use of whole plant cannabis as a medicine from all other forms of evidence. CBD is also an excellent example that justifies drawing a distinction between cannabis and specific cannabinoids. Other exclusions are preclinical data, which may show promise in whole animal or tissue cultures, but cannot be presumed to translate to humans.

6.1 Overview of safety, efficacy standards: Several countries (including Canada, Netherlands, Israel) and 23 of 50 states in the United States have permitted the use of cannabis for medicinal purposes, with or without undergoing a systematic medicines approval process. In this update on the current status of cannabis as a medicine, a simple question is addressed: "are clinical trials that report cannabis-induced therapeutic benefit sufficient to establish currently accepted medical use?" Globally, the efficacy, safety and quality of the medical products on the market in countries have benefited enormously from a robust scientific and evidence based process. This should continue to be the central organizing principle in evaluating and approving substances for use as medicine.

By following a rigorous process, the scientific, medical, and public community can be confident that decisions are made on the basis of scientific data and judgment. This is the hallmark of an effective system for protecting the public. If cannabis is subjected to the same criteria as all medications, the medicines approval process would require that clinical trials be designed and conducted in a way that provides regulatory agencies with the necessary scientific data upon which they can make approval decisions. Without official approval, there would be no requirements for post-marketing surveillance and reporting of adverse events. Accordingly, the adverse consequences of cannabis, as outlined in Section 5 above, are based largely on cannabis used for recreational purposes, even though concerns of cannabis' adverse effects when used for medical purposes are rising.[214,215,216]Also, contrary to modern medications, cannabis is a complex mixture of hundreds of chemicals of unknown concentrations, pharmacological

effects, and side-effects, delivered mainly by a currently unprecedented and controversial route of administration for medicines, smoking or vaporization (see discussion at section 6.2.3 below).

6.2 Cannabis: overview of dosing, entourage and administration

6.2.1 ***Cannabis chemistry and dose*****.** Cannabis is a complex substance containing multiple cannabinoids and other compounds, and their typically wide range of THC or CBD concentrations challenge assessment of therapeutic efficacy. In order to objectively evaluate the effects of cannabis, it needs to be provided by a source with reproducible methods of production delivering controlled levels of cannabinoids. Only by systematic evaluation of known doses of pure or purified compounds or extracts, and possibly by designing more effective variants, can the field advance without compromising the rigors of the modern drug approval processes. Yet a safe therapeutic window for cannabis has not been established, and clinical trials (see below) have studied cannabis across a number of THC concentrations (1-23%). The ratio of THC to CBD has been rising in the cannabis plant.[217] In controlled clinical trials with cannabis, THC or CBD levels are usually the only composition of matter reported. These two cannabinoids produce distinct, and in some cases, opposite effects, a relationship that underscores the need to isolate individual cannabinoids and investigate them separately.[218]

Because cannabis is a botanical product, there are other substantial obstacles to meeting the statutory standard for approval. In the context of cannabis, the most active psychoactive constituent, THC, is known, but it is unclear how to evaluate the effects of the other 750 chemicals in the plant including the 104 cannabinoids of which the majority have unknown effects, interactions, and side effects.[219,220] Cannabis smoke contains significant amounts of toxic chemicals, including ammonia, hydrogen cyanide and nitric oxide.[221] The doses of active ingredients are unknown to patients and physicians, and for some preparations, there is no assurances of product purity or absence of microbes or pesticides that can produce disease.[222,223]

6.2.2. ***Entourage effect*****:** A widely held and user-reported belief is that the benefit of smoking the whole plant product provides more relief than orally-administering the isolated cannabinoids, a belief referred to as the "entourage effect".[224] This is not a trivial issue, as it is a motivating force for whole cannabis plant to be used for medical purposes in lieu of isolated compounds. Conceivably, at least three explanations may contribute to these self-reports:
(1) CBD may ease THC-induced anxiety or psychosis and their combination results in a more satisfying net effect.
(2) Pharmacokinetics may account for some of these perceived differences. Smoking produces immediate effects much faster than oral consumption, and dose can be precisely and rapidly titrated (but likely the euphorigenic effects are concurrently maximized). On the other hand, oral consumption typically results in a longer duration of effect than does smoking, conferring a possible advantage to peroral isolated cannabinoid administration. For example, a clinical trial comparing the effects of smoked cannabis with dronabinol (THC alone) suggested that, under controlled conditions, cannabis and dronabinol decreased pain, but dronabinol produced longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than cannabis.[225] In another pilot study, caloric intake and body weight were measured in HIV-positive cannabis smokers, and compared with placebo or dronabinol. Cannabis and dronabinol effects were comparable, with both dronabinol and cannabis well-tolerated and producing substantial and comparable increases in food intake.[226] All cannabinoid conditions produced significant intoxication, except for low-dose dronabinol. No other clinical trials have compared smoked cannabis to oral/spray THC or THC/CBD for other medical conditions, and few clinical trials compare cannabis with alternative existing, medications, leaving the issue of whether smoked cannabis confers an advantage in efficacy and safety unresolved.

(3) Cannabinoids are not the only products of the cannabis plant with putative medicinal properties. Cannabis terpenoids share a precursor to cannabinoids (e.g. limonene, myrcene, α-pinene, linalool), some of which are under investigation as candidate therapies or as facilitators of cannabinoid efficacy. Evidence is needed to prove the validity of the widely held belief and self-reporting, that whole plant cannabis is superior to isolated compounds because of synergism between various components.

6.2.3. ***Smoking and vaporization*****:** It is generally recognized that smoking can be harmful to health.[227] Standard medicines are not delivered as inhaled smoke, but enter the body by other forms and routes of administration (pill, injection, topical creams, patches, inhalants, eye drops, liquid drinks, suppositories). Clinical trials measure pharmacokinetic, pharmacodynamic properties of each drug, along with metabolic rates and metabolites. To confound clinical results with cannabis, the percent of THC that enters the body is variable depending on the type of smoking ritual.[228,229,230] Smoking remains a controversial route of delivery, even with a recent report that found no major changes in spirometric measures of lung health of light, but not heavy, recreational cannabis smokers.[231] Nearly all cross-sectional and longitudinal studies evaluating cannabis use association with chronic respiratory symptoms (cough, phlegm, wheezing and breathlessness) have found a positive relationship of active smoking with symptoms of chronic bronchitis (mainly cough and phlegm) although not with shortness of breath or lung cancer. However, possible cancer risks remain for heavy smokers.[232,233] Whether vaporizing cannabis is a safer alternative to smoking remains uncertain, as health benefits derived from reducing toxic smoke components, (except in persons with chronic lung disease), need to be weighed against hazards of acute intoxication and long term consequences to the brain. Two studies with vaporized cannabis showed modest relief of neuropathic pain,[234,235] with one at a very low dose of THC (1.29%). In support of this method of delivery, vaporized or smoked cannabis yielded similar maximal blood levels indicating similar delivery efficiency, but a wide range of inter-subject blood levels of THC.[236] Given similar blood levels from both routes of administration, is it not surprising that CB1 receptor activation was comparable with smoked or vaporized sources of THC.[237]

6.3 Safety

6.3.1. ***Missing safety data:*** Isolated cannabinoids have undergone a number of RCTs documenting safety, efficacy and side effect profiles as required in a formalized drug approval process, whereas few RCTs are reported for whole plant cannabis. In the absence of long term clinical trials, most data by necessity is extrapolated from recreational users. In the literature, it was not possible to identify trials of long duration that investigate outcomes in people using cannabis long-term for medical conditions, even though cannabis is used primarily by people with chronic medical conditions (e.g. AIDS neuropathy, AIDS wasting, multiple sclerosis, chronic pain, seizures, others). Current estimates are that 25-50% of daily cannabis users develop an addiction to cannabis.[238] On the basis of current information and especially in view of negative side effects of chronic use (addiction, compromised cognition and executive control), one cannot be assured that cannabis can be safely used under medical supervision for long term open-ended use.

Key information about side-effects and safety would be collected if cannabis went through the normal evaluation process for approval as a medicine. Of RCTs, the majority of trials do not report a full dose-response evaluation, inclusion criteria generally require subjects to be experienced cannabis users, trials are of short duration (days to weeks, not 6-12 months), the sample populations are low, they do not assess quality of daily life or function when using a psychoactive substance (e.g. driving, work quality, school attentiveness, cognitive impairment) or effects after prolonged use (e.g. addiction, cognition, executive function, motivation, psychosis).

6.3.2. ***Medical conditions with cognitive decline****:* Side effects of cannabis have to be viewed in the

context of immediate effects and after repeated long term use. In research of subjects under the influence of cannabis, dose-related impairments of immediate and delayed recall of information can be quantified. Various phases of learning and memory can be affected, as well as signs of depersonalization, distorted sensory perception, and altered time perception. Executive function in cannabis users (attention, concentration, decision-making, impulsivity, self-control, reaction time, risk taking, verbal fluency and working memory) is impaired acutely in a dose-dependent manner.[239] Regular cannabis use for medicinal purposes is a relatively recent regimen that its long-term effects on seriously ill people is comparatively unknown, especially among those harboring disease-related cognitive decline (e.g. cancer, HIV/AIDS, multiple sclerosis, Alzheimer's, Parkinson's disease, certain seizure disorders). An illustration of this is in cancer, where chemotherapy promotes cognitive decline before, during or after, with memory loss, loss of concentration and attention the most frequent symptoms.[240, 241] Conceivably, the combination of chemotherapy and cannabis reduces cognitive functions in additive or synergistic ways. Yet the impact of cannabis on parameters of cognition has not been tested, although the number of patients using cannabis during chemotherapy is growing. For multiple sclerosis, another disease beleaguered by cognitive impairment, it is now recognized that cannabis worsens cognitive deficits.[242] Reports on cannabis-induced relief of physical symptoms in other neurodegenerative disorders with cognitive impairment (Parkinson's disease, Alzheimer's disease), do not judiciously measure cognition. Cannabis may compromise quality-of-life for these populations but this parameter remains inadequately explored.

6.3.3 ***Long term effects****:* A significant number of individuals report paranoia, persecutory ideas, or hallucinations while under the influence of cannabis[243] and with drug-naïve study subjects, high drop-out rates would compromise the integrity of the clinical trial. For chronic users, other side effects can include altered brain structure and brain circuits impaired short-term memory, compromised judgment and decision-making, and mood effects that can range from severe anxiety manifest as paranoia or even psychosis, especially after high-doses, as reviewed earlier. Cannabis can reduce motor coordination alone, or combined with alcohol, slow the reaction time of drivers.[244] Cannabis smoking can cause or worsen breathing problems such as bronchitis or chronic cough and evidence is increasing that it may cause serious cardiovascular problems in some users.[245] The impact of long-term use on young people, whose frequent use for asserted medical reasons is increasing rapidly, cannot be adequately predicted at this time either.

There are no recent clinical trials in a sufficiently large cohort of cannabis-naïve subjects with a specific medical condition to conclude that there is an acceptable level of safety for use of cannabis under medical supervision.

6.4 Evidence of Cannabis for Medicinal Use

6.4.1 ***Use of cannabis for specific purposes, internationally:*** A recent, international survey of 31 countries investigated self-reported medicinal use of cannabis (and cannabinoids). Respondents (953) from the United States, Germany, Canada, France, the Netherlands, and Spain were generally male (64%), relatively young (mean age 40.7 years) with a smaller cohort using over the age of 51 (24%), and far fewer past the age of 60 or 70 (6%, 1%). Cannabis was used primarily for back pain (11.9%), sleeping disorders (6.9%), depression (6.7%), injury or accident-generated pain (6.2%), and multiple sclerosis (4.1%).[246] With the exception of multiple sclerosis, and neuropathic pain, randomized controlled trials with cannabis use for these symptoms are scant.

It is within reason to acknowledge that certain people report relief and symptom improvement while under the influence of cannabis, as corroborated by surveys, case-based studies, anecdotal self-reports, laboratory-based short-term trials. Evidence from RCTs is presented below, with sources from primary manuscripts and 10 meta-analyses.[247,248]

It should be noted that the psychoactive responses engendered by cannabis confound clinical research, as it is a significant obstacle to designing randomized, double-blinded clinical trials. Nor are there adequate, well-controlled double-blinded long-term RCTs demonstrating efficacy in drug-naïve populations compared with cannabis-using populations.[249] The majority of RCT trials recruit experienced cannabis using subjects for a number of reasons, including concerns of unacceptably high drop-out rates among cannabis-naïve subjects.[250]

6.4.2 ***Neurological diseases or symptoms***

Several recent reviews and meta-analyses have weighed in on the therapeutic indications for neurological diseases.[251, 252, 253, 254] Many degenerative neurological diseases and certain pain conditions are characterized by cognitive impairment or decline, in addition to physical signs of impairment. A characteristic consequence of smoked cannabis is to compromise cognition. This effect needs to be considered in weighing the risks-benefits of cannabis.

6.4.2.1 Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory, autoimmune, degenerative disease of the central nervous system.[255] It is among the most common causes of non-traumatic neurological disability in young adults of northern European descent.[256,257] Globally it affects about 2-3 million people,[258] with incidence particularly high in Northern Europe and other countries settled by Northern Europeans. The consequence of neuronal loss is the development of pain, spasticity, incontinence, cognitive decline, limb tremors, fatigue, sleep disturbances and all of which impact quality of life.[259,260] One study from the United Kingdom reported that approximately 14-18% of MS patients used cannabis for symptom relief from pain, spasticity and insomnia.[261] Given that cognitive impairment occurs in approximately 40-60% of patients with multiple sclerosis, is associated with structural and functional brain changes,[262,263] and given the effects of MS on cognition, patients who smoke cannabis may be particularly vulnerable to cognitive deficits and brain changes attributed to cannabis. MS patients who smoke cannabis display additional deterioration in measures of cognition, including processing speed, memory, executive functioning, and deficits in recruiting brain regions during a memory task.[264,265,266] Furthermore, cannabis use by MS patients resulted in more wide spread cognitive deficits. The deficits correlated with loss of tissue volume in subcortical, medial temporal and prefrontal regions. Reductions in brain volume were associated with more extensive cognitive impairment in the cannabis-using MS population compared to the non-cannabis MS group. This association between cannabis use, cognitive impairment and structural brain changes in MS patients[267] is a cautionary example of the multiple factors to consider along with the therapeutic potential of cannabis.

There is some evidence that the endocannabinoid system is dysregulated in MS.[268] In an animal model of MS, the neurodegeneration rate can be reduced by administration of CB2 agonists, exogenous 2-arachidonoylglycerol (2-AG) administration, or elimination of the major degrading enzyme FAAH, in transgenic mice.[269,270,271] 2-AG is a full agonist at the human CB2 receptor, whereas anandamide is a weak partial agonist and local concentrations may even temper 2-AG actions.[272] To date there are no reports of clinical trials testing the efficacy of modulating endocannabinoid levels neither for symptom relief nor neuroprotection. Cannabinoid agonists (THC, Sativex®) alleviate the symptoms,[273,274] but evidence that cannabinoids can function as neuroprotective agents is weak, as THC failed to attenuate MS progression or disability.[275] MS is characterized by a wide range of cognitive and physical symptoms; clinical trials with cannabis need to consider whether cannabis improves or compromises a range of symptoms, including cognition, simultaneously and whether the costs outweigh the benefits of treatment.[276]

Randomized controlled trials with cannabis: Three RCTs were identified which used inhaled or vaporized cannabis to treat MS symptoms.

1. A double-blind randomized placebo-controlled study of inhaled cannabis smoke on postural responses was performed in 10 adult patients (five female, five male) with spastic MS and 10 normal volunteers matched for age, sex, and weight. A computer-controlled dynamic posturographic platform measured platform movements. Smoking one cannabis cigarette (1.54% THC) increased postural tracking error in both the patients and normal control subjects, with eyes open or shut. Tracking errors were higher for patients than controls and response speed of the patients was lower, with eyes closed. The conclusion of the study investigators was that cannabis smoking worsens posture and balance in MS patients.[277]

2. Spasticity is a common and poorly controlled symptom of multiple sclerosis. In this placebo-controlled, crossover trial, adult patients with multiple sclerosis and spasticity were randomly assigned to either smoked cannabis (4% THC), once daily for three days, or to identical control placebo cigarettes, once daily for three days.[278] After a washout interval of 11 days, participants crossed over to the opposite group. The primary outcome was change in spasticity measured by patient score on a modified Ashworth scale. Secondary outcomes included: (a) patients' perception of pain (visual analogue scale), (b) a timed walk, (c) cognition, and (d) ratings of fatigue. Of 37 participants, 80% were experienced cannabis users, and 30 completed the trial. Seven subjects dropped out of the study, the majority cannabis-naïve. Treatment with smoked cannabis resulted in a reduction in Ashworth scale ratings of spasticity, patient self-reports of spasticity, of pain, and a significant reduction in cognitive function. Walk times did not change. Dizziness (23%), headaches (20%), fatigue (20%) nausea (11%), too "high" (6%) were reported side effects. Authors concluded that smoked cannabis was superior to placebo in spasticity and pain reduction in participants.

3. Another RCT may reside on the "margins" of this review, because oral THC was compared with an oral "cannabis sativa extract", but no information is provided on whether the extract is analogous to nabiximols (excluded from this survey), or is a crude extract of whole plant cannabis containing its constituents. [279] This randomized, double-blind, placebo-controlled, twofold crossover study was conducted in 16 patients with MS for four weeks. Both drugs were safe, but adverse events were more common with plant-extract treatment, compared with THC. Compared with placebo, THC or plant-extract did not reduce spasticity. Both THC and plant-extract treatment worsened the participant's global impression.

6.4.2.2 Neuropathic pain

Pain can be classified as acute or chronic, or by site of origin (nociceptive) or nerves (neuropathic). Neuropathic pain occurs in various disease states (e.g. diabetes, HIV/AIDS, post-traumatic pain, cancer, excess alcohol use, rheumatoid arthritis) and can be a persistent, debilitating condition. HIV neuropathic pain affects 30% or more of HIV-infected individuals and some antiretroviral therapies can worsen the condition. Current analgesics and other medications offer incomplete pain relief. HIV-infected individuals report improvements in health from smoking cannabis. Of over 200 people with HIV/AIDS, 23% used cannabis in the previous month.[280,281] The association between cannabis use for psychoactive purposes and cannabis used medically for HIV/AIDS is relevant,[282] with considerations including cognitive impairment, as both cannabis use and duration of HIV infection may affect cognitive functioning that may impair their ability to follow important treatment guidance.[283,284] While evidence for an effect of inhaled cannabis on chronic neuropathic pain is promising, trials followed their patients for a maximum of two weeks. Long-term trials, which also examine pragmatic outcomes, are needed to increase confidence that short term trials, conducted largely in experienced cannabis users, are relevant to an overall cost-benefit analysis of long term cannabis use to treat chronic neuropathic pain.

Randomized controlled trials with cannabis:

Six recent manuscripts were identified reporting randomized controlled clinical trials with smoked or vaporized cannabis. Five were recently summarized positively in a review co-authored by investigators of the primary studies.[285] The pilot studies showed beneficial effects on alleviating pain, and by inhalation,

enabled patients to titrate the effects. Yet these six reports did not establish a conclusive dose effect vs adverse events therapeutic window, as doses used varied. Acceptable limits of cognitive impairment were not described and no report addressed cognitive impairment outside a clinical research setting. Others have reviewed the overall evidence for cannabis and cannabinoids for pain.[286,287] No RCTs are reported for ingested cannabis, which displays variable onset times, inability to titrate doses, and more side effects.[288] Edibles containing cannabis, because of pharmacokinetic differences, may be more likely to induce psychosis, which may outlast the period of intoxication.[289,290] The peak serum concentration of orally absorbed THC is delayed compared with inhaled administration and is not reached until one to three hours have elapsed. If more than the suggested serving size is consumed (e.g. > THC 100 mg) because users felt no effect and did not wait three hours for THC to be absorbed, they may undergo acute toxicity. Differences in oral metabolism are likely play a role in the development of acute psychosis in these patients who regularly smoke cannabis. Oral administration produces the active metabolite (11-OH-THC), which is proposed by Favrat et al to reach the target (CB1 receptor) more efficiently.[291]

1. Diabetic neuropathy (1%, 4%, 7% THC):
A randomized, double-blinded, placebo controlled crossover study in 16 patients with painful diabetic peripheral neuropathy assessed the short-term efficacy and tolerability of inhaled cannabis.[292] There was a modest reduction in spontaneous pain for the low and moderate dose but a marginal effect at the highest dose (% reduction in pain: placebo 61.2%; 1% THC: 66.7%; 4% THC: 70.3% and 7% THC: 65.5%) The high dose impaired cognition, and the moderate and high doses elicited euphoria or somnolence. The time to minimum pain was not dose-dependent. The report is inconsistent with another study showing pain improvement only at 9.4% THC.[293]

2. HIV-associated sensory neuropathy (3.5% THC):
This study measured the effect of smoked cannabis on neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model.[294] Primary outcome measures included ratings of chronic pain and the percentage achieving 30% reduction in pain intensity. Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group, with findings comparable to oral drugs used for chronic neuropathic pain. Adverse events were of far higher prevalence in the cannabis than the placebo group and included anxiety, sedation, confusions, dizziness, disorientation, paranoia and nausea, with most achieving robust statistical significance. It is not possible to exclude relaxation and euphoria from the pain relief.

3. Neuropathy: low to moderate doses (1.29%, 3.53% THC):
Wilsey et al[295] conducted a similar study with smoked cannabis and then followed up in a larger cohort, assessing vaporized cannabis in a broader range of neuropathies with two doses of THC (1.29% and 3.53%) compared with placebo.[296] Both active study medications provided statistically significant 30% reductions in pain intensity, comparable to two commonly used anticonvulsants used for neuropathic pain treatment. Psychomotor tasks revealed significant cannabis impairment at 60 minutes and at four hours, with performance worse at the higher THC dose. The author concluded that cannabis effects "on learning and memory, where effect sizes were in the small to medium range, were unlikely to have significant impact on daily functioning". Although earlier work suggested that frequent cannabis users become tolerant to cannabis-related performance-impairing effects, more recent comparisons of cannabis-related effects on cognitive performance of frequent users suggest impairment on a variety of cognitive tasks, which may be dose and age-dependent.[297]

4. HIV/AIDS neuropathy (1-8% THC):
Ellis et al[298] also assessed smoked cannabis for HIV/AIDS neuropathy in a cross-over design. Among 28 completers (27 experienced cannabis users), pain relief was greater with cannabis than placebo, with 46% achieving at least 30% pain relief with cannabis versus placebo (18%). Most side effects were mild and self-limited, but two subjects experienced treatment-limiting toxicities. Smoked cannabis was generally

well tolerated and effective when added to concomitant analgesic therapy with medically refractory pain. Analgesia duration was not assessed in this short-term study. Concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst were reported side effects.

5. Neuropathy (2.5-9.4% THC):
Ware et al[299] tested three doses of smoked cannabis for chronic neuropathic pain (2.5%, 6%, 9.4% THC) in which 18/24 were experienced cannabis users. Euphoria or "high" was reported on three occasions throughout the trial, but there was no evidence of euphoria during the three hours following the first dose of each cycle regardless of THC potency. Finally, a study explored the pharmacokinetics, safety, tolerability, efficacy, and ease of use of a portable thermal-metered-dose inhaler for cannabis in a cohort of eight patients with chronic neuropathic pain on a stable analgesic regimen including cannabis.[300] A significant 45% reduction in pain intensity was noted at 20 minutes post inhalation, returning to baseline within 90 minutes. Tolerable, lightheadedness, lasting 15-30 minutes was the only reported adverse event.

6.4.2.3 Alzheimer's Disease
Alzheimer's disease (AD) is the most common type of dementia, and is characterized by a number of debilitating symptoms, including cognitive decline, sleep disorders, and behavioral changes.[301] There is some interest in assessing the therapeutic potential of cannabinoids in AD, especially for sedative effects or sleep disorders. Assessment of memory and cognitive function as outcome measures with long term use of cannabinoids is critical, as this class of drugs affects memory, cognitive functions, and balance in frail older people. There are no RCTs with whole plant cannabis to treat symptoms of Alzheimer's disease or progression of the disease.[302] Some intriguing positive benefits relevant to the degenerative process are derived from cellular or imperfect animal models.[303] Four RCTs are reported with isolated cannabinoids, but little is known about safety in this population, especially as long term exposure to cannabinoids increases the risk of psychiatric disorders and dysfunction (e.g., cognitive abnormalities, psychotic, mood disorders).

6.4.2.4 Other Neurological Conditions
- Epilepsy: There are no reported RCT with cannabis use in any form of epilepsy.[304]
- Huntington Disease Dyskinesias: There are no RCT with cannabis for this condition.
- Parkinson's Disease (Levodopa-Induced Dyskinesias): There are no RCT with cannabis for this condition.[305] A recent an open label trial reportedly found positive improvements in Parkinson's disease patients that smoked cannabis.[306] Others recommend more research with isolated cannabinoids.[307]
- Cervical Dystonia: There are no RCT with cannabis for this condition.
- Tics of Tourette Syndrome: There are no RCT with cannabis for this condition.

6.4.3. *AIDS Wasting, Cachexia and Appetite Enhancement*
Studies have shown that smoked or ingested cannabis, either as a botanical or a synthetic THC (dronabinol), improves appetite, increases weight, and improves quality of life in HIV/AIDS patients. Seven RCTs with smoked cannabis or individual cannabinoids of short duration (21-84 days) were identified for the treatment of AIDS in a small number of patients.[308] Other measured changes included viral load, weight, body fat, appetite, caloric intake nausea and vomiting, performance and mood.

6.4.3.1 AIDS viral load
Cannabis (3.95%), dronabinol or placebo had no adverse effect on viral load or protease inhibitor pharmacokinetics.[309] Smoked and oral cannabinoids appeared safe in people with HIV infection in the short duration of the study (21 days).

6.4.3.2 AIDS and appetite

Appetite enhancement is indicated in diseases characterized by loss of appetite and wasting. Tolerability and efficacy of smoked cannabis (1.8%; 2.8%; 3.9% THC) and oral dronabinol in HIV-positive cannabis smokers was compared in those with and without a clinically significant loss of muscle mass, component of AIDS wasting. Cannabis and the lower dronabinol doses (10, 20 mg) were well tolerated (e.g. few physical symptoms e.g. nausea, dizziness, intoxication, headache, significant increases in ratings of "good drug effect") in both groups of participants. Cannabis and dronabinol significantly increased caloric intake in the low bioelectrical impedance analysis (BIA) group but not in the normal BIA group. (BIA estimates total body water, a measure of fat-free body mass). Drug effects on cognitive performance were designated as minor. The study was compromised as subjects were allowed to use cannabis at home throughout the study (no regulated doses), with cannabis prohibited on the morning of testing. For experienced cannabis smokers with clinically significant muscle mass loss, both dronabinol and cannabis produce substantial and comparable increases in food intake without producing adverse effects.[310] These findings question the need for a smoked product if there is an approved medicinal product which is equally effective.

6.4.3.3 HIV/AIDS and appetite, mood, cognitive performance, physiologic measures, sleep

A placebo-controlled within-subject design evaluated cannabis and dronabinol across a range of behaviors: HIV-positive cannabis smokers (n=10) completed two, 16-day inpatient phases.[311] Each dronabinol (5 and 10 mg) and cannabis (2.0%, 3.9% THC) dose was administered four times daily for four days. Compared with placebo, cannabis and dronabinol dose dependently increased daily caloric intake and body weight in HIV-positive cannabis smokers. All cannabinoid conditions produced significant intoxication, except for low-dose dronabinol (5 mg), with intoxication rated as "good drug effect". There was no impairment of cognitive performance. Effects of cannabis and dronabinol were comparable, except that only cannabis (3.9% THC) improved ratings of sleep. These data suggest that for HIV-positive cannabis smokers, both dronabinol (at doses eight times current recommendations, likely because of tolerance due to prior heavy cannabis use), and cannabis produced substantial and comparable increases in food intake. A sustained effect of cannabis on AIDS-related morbidity, mortality, safety in patients on effective antiretroviral therapy has not been shown. The available evidence is insufficient or low quality[312] to alter medical and regulatory guidance.

6.4.4. ***Cancer and symptom management*****:** Cannabis has been proposed to alleviate symptoms of cancer, including reduced appetite, chemotherapy-induced nausea and vomiting, pain and even to attenuate the disease process.

6.4.4.1 Cancer, chemotherapy and anti-emesis. Chemotherapy-induced nausea and vomiting were inadequately controlled in the 1960s and 1970s, motivating investigation of the anti-emetic properties of cannabinoids and leading to the approval of nabilone and synthetic THC (dronabinol). There have been only three small clinical trials on the use of cannabis in cancer patients.[313] All three studies assessed antiemetic activity, with different patient populations and chemotherapy regimens. One study demonstrated no effect, the second study showed a positive effect versus placebo. The report of the third study did not provide enough information to characterize the overall outcome as positive or neutral. There are no published data on the use of cannabis for other cancer-related or cancer treatment-related symptoms.[314]

Some patients prefer smoked cannabis over oral cannabinoids, with rationales that include ability to self-titrate smoked cannabis, the swallowing of pills is difficult while experiencing emesis, onset of relief is faster with smoking, and the whole plant ("entourage") is more effective.[315] Side-by-side clinical trials with oral cannabinoid compared with smoked cannabis in HIV/AIDS (see above) show scant evidence for

therapeutic advantage of smoked cannabis. Furthermore, if the goal is to prevent nausea, factors such as speed of brain entry, challenges of swallowing pills while vomiting, dose titration, are not important factors; an oral cannabinoid can be administered long before chemotherapy to avoid its unpleasant side effects. Inhaled cannabis engenders a higher rate of brain entry and associated undesirable side effects, which can include intoxication, anxiety, acute psychotic reactions, and orthostatic hypotension.[316] Recent drug discovery programs have introduced newer anti-nausea drugs that are superior to cannabinoids in clinical trials. It is also possible that non-psychoactive isolated cannabinoids may prove to be effective for nausea and vomiting.[317] A significant proportion of older cancer patients with no previous cannabis experience refused to continue its use because they found the psychoactive effects too unpleasant. For such reasons, there is doubt whether smoked cannabis will find widespread clinical application, except among those who have previously used it for nonmedical purposes.[318] Paradoxically, cannabinoids can be both anti-emetic and pro-emetic. A cannabinoid hyperemesis syndrome has recently been described in which persistent and regular cannabis use (i.e., daily or weekly use for more than one year) is associated with episodic nausea and vomiting[319] and nonresponse to treatment for cyclic vomiting other than hot showers.[320]

6.4.4.2 Cannabis, symptoms and anti-tumor activity: At present, data show contradictory results.[321],[322] The promise of cannabinoids as anti-tumor agent stems from preclinical research, using either cultured cells derived from human or rodent tumors, or mouse tumor models. These initial studies are insufficient to satisfy stringent criteria for recommending cannabis to test human cancers. Cell cultures have yielded contradictory results, with THC potentiating or inhibiting tumor proliferation, as a function of tumor type and its pathology. In one small Phase I trial of nine patients with aggressive glioblastoma multiforme treated with direct infusions of THC,[323] THC did not extend the life span of these patients.

6.4.5. *Crohn's Disease*

There is evidence that cannabis use is higher in patients with inflammatory bowel diseases,[324] but until recently, these reports were not subjected to controlled trials. In a prospective trial to determine whether cannabis can induce remission, 21 cannabis-naïve patients with Crohn's Disease who did not respond to therapy with steroids, immunomodulators, or anti-tumor necrosis factor-α agents were assigned randomly to groups given cannabis cigarettes (THC, 23%; less than 5% CBD) twice daily or placebo cannabis (with THC extracted) for eight weeks of treatment and two weeks thereafter. Complete remission was achieved in five of 11 subjects in the cannabis group (45%) and one of 10 in the placebo group but this was not statistically significant. A positive clinical response was observed in 10 of 11 subjects in the cannabis group and in four of 10 in the placebo group. Three patients in the cannabis group were weaned from steroid dependency and subjects reported improved appetite and sleep, with no significant side effects. After an additional 2-week washout period, the mean self-reported scores of the cannabis group rebounded to pretreatment levels, and at 10 weeks there was no difference in mean rating scale results between the placebo and cannabis groups. The authors concluded that cannabis use produced a clinical, steroid-free benefit in patients with active Crohn's disease, but the results were not statistically significant. No independent measures (e.g. endoscopy) were performed to confirm self-reported improvements in the disease state. The primary end point of the study, induction of remission, was not achieved but this short course (8 weeks) of THC-rich cannabis produced clinical, steroid-free benefits to patients with active Crohn's disease, compared with placebo, without side effects.[325] Intriguingly, there was no difference between experimental and placebo groups in side effects, including sleepiness, nausea, and confusion, memory impairment concentration, despite a 23% THC concentration. Patients denied any withdrawal symptoms when stopping cannabis use at the end of the study. Whether this reflects a reduction of inflammation or only amelioration of symptoms, such as a reduction in pain and improved appetite, remains unclear. Cannabis may conceivably reduce inflammation indirectly by reducing stress, but symptomatic improvement without a reduction in inflammation could cause ongoing intestinal structural damage.

6.4.6. *Post-traumatic stress disorder (PTSD)*

Post-traumatic stress disorder (PTSD) is a state of mind activated by either witnessing or experiencing a shocking, frightening, horrifying episode(s). If symptoms continue or get worse after prolonged periods of time (months or years later), interfere with daily life and function, and persist long after there is no danger of a recurrence, the condition is designated as PTSD. There are no large scale RCTs with cannabis to alleviate PTSD symptoms. On the contrary, cannabis use may impede the effectiveness of treatment for PTSD, and is associated with poorer clinical outcomes with PTSD.[326,327]

6.4.7. *Glaucoma*

Glaucoma is an array of ocular disorders which leads to visual deficits or blindness.[328] Elevated intraocular pressure (IOP) is a primary cause of vision loss. Cannabis lowers blood pressure and may also reduce aqueous humor production via cannabinoid receptor activation, pharmacological actions that temporarily reduce IOP.[329,330,331] A reduction in blood pressure can be both helpful and harmful as reduced blood perfusion may compromise optic nerve function. Because of its short duration of action on blood pressure, it is necessary to smoke cannabis six to eight times each day to achieve a constant decrease in IOP, which conceivably will compromise daily function, impair cognition in the elderly, and with continuous use, initiate progression to addiction in the vulnerable[332]. Another challenge to using cannabis is the development of tolerance to its pharmacological actions in the eye,[333] which raises significant concerns about the cost-benefit for its use in treating glaucoma. An alternative approach is to focus on modulating the endocannabinoid system, which may circumvent the toxic and adverse effects of cannabis.[334] Cannabinoids failed to reduce IOP in glaucoma patients in a small clinical trial.[335]

Summary and Conclusions

It has been advanced that whole plant cannabis can be used for multiple therapeutic purposes. The evidence presented on potential medical uses and risks of cannabis in humans herein is focused on unprocessed, botanical cannabis and not isolated cannabinoids, some of which are medically approved. The medical benefits of cannabis continue to be debated globally, as they have been for nearly 150 years. Cannabis extracts were listed in the British, and later in the US Pharmacopeia for sedative and anticonvulsant effects, but were removed a century later, for similar reasons that fuel the current debate. The movement to revive cannabis as a medicine to alleviate pain, seizure disorders, enhance appetite, and relieve a myriad of other neurological or metabolic diseases, is driven by multiple factors. These include inadequacies in current medications to treat specific symptoms or diseases, along with self-reported benefits derived from cannabis.

With the discovery of the endocannabinoids and their receptors in the brain and other tissues, the rationale for, and research of medicinal effects of cannabis or isolated cannabinoids has entered a modern context. In brain, endocannabinoids and their receptors play a fundamental role in regulating pleasure, memory, thinking, concentration, body movement, awareness of time, appetite, pain, sensory processing (taste, touch, smell, hearing, and sight), and brain development. In peripheral tissuess, the widespread distribution of endocannabinoid signaling systems conceivably account for the myriad effects and therapeutic potential of cannabinoids. Especially for psychoactive drugs such as cannabis, rigorous criteria for its approval as a safe and effective medicine need to be fulfilled, along with a meticulous cost-benefit analysis to weigh its therapeutic potential alongside it detrimental effects to individuals and to society.

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