Cannabis and Medicinal Properties

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http://www.who.int/substance_abuse/publications/cannabis/en/

Terminology

Marijuana. The term marijuana is used instead of cannabis. Its use for medicinal, ritual or recreational purposes results from the actions primarily of cannabinoids in the cannabis plant.

Cannabinoids. Cannabinoids are basically derived from three sources: (a) *Phytocannabinoids* are cannabinoid compounds produced by plants *Cannabis sativa* or *Cannabis indica* or *Cannabis ruderalis;*[1]
(b) *Endocannabinoids* are neurotransmitters produced in the brain or in peripheral tissues, and act on cannabinoid receptors (CB); altering metabolism or CB function can affect cannabinoid function.
(c) *Synthetic cannabinoids*, synthesized in the laboratory, are structurally analogous to phytocannabinoids or endocannabinoids and act by the same biological mechanisms.

A focus on marijuana and not isolated cannabinoids

The evidence presented on potential medical uses and risks of marijuana in humans focuses on unprocessed, botanical or dispensary marijuana and not isolated cannabinoids, some of which are medically approved following quality clinical trials. The restricted review is based on the use of whole plant or concentrated marijuana dispensed in various preparations, for treating illnesses or symptoms. The plant contains at least 750 chemicals, among which are some 104 different cannabinoids.[2,3] Boundaries between marijuana and isolated cannabinoids are based on the following considerations: (a) to avoid confusing whole plant with approved, isolated cannabinoid terminology; (b) the composition, purity, bioavailability, pharmacokinetics and pharmacodynamics of botanical marijuana (delivered via smoke inhalation, vaporization, liquids, foods, creams) differs from extracts or purified individual cannabinoids delivered orally; (c) the bioavailability of active cannabinoids in marijuana, e.g. delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are unpredictable because of their various concentrations in dispensary marijuana, differences in smoking, vapor inhalation or ingestion between users, form of product, and types of delivery systems. In contrast, a fixed, known oral dose of a cannabinoid can be yield relatively predictable levels in plasma or whole blood samples; (d) to avoid extrapolating conclusions drawn from meta-analyses and primary sources reporting efficacy from randomized controlled trials (RCT) of purified and medically approved cannabinoid formulations at known, fixed doses. Approved cannabinoids are oral or sublingual spray preparations, whereas marijuana is used predominantly by smoking or vaporizing, a rapid form of brain delivery acknowledged to be a route of administration with higher addiction potential (see Pharmacokinetics, below); (e) to avoid extrapolation and appropriation of safety data generated from isolated and medically approved cannabinoids (with known, relatively low doses) to whole plant marijuana, for which there are no guidelines for doses and no packet insets providing adverse effects, precautions, or warnings.

As the concentration of THC or CBD in marijuana is not fixed, with THC levels rising and CBD levels declining, increasing, adverse events such as psychosis, anxiety, hallucinations are problematic. 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, documented side effects, other criteria), is beyond the scope of this summary. At times, information on specific cannabinoids may be included, if comparisons with botanical marijuana are instructive. Approval of marijuana to treat qualifying conditions is driven essentially by small RCT, surveys of low or moderate quality, self-reports, preclinical studies in vitro or in animals, testimonials, anecdotes delivered in state houses or court rooms, ballot or legislative initiatives, and by advocacy groups. This approach has

circumvented the rigorous FDA drug approval process and is akin to a mostly unregulated alternative treatment/herbal remedy market.

THC and CBD are instructive. The isolation and purification of THC and CBD from the marijuana plant have revealed distinctions in the mechanisms of action of THC, its psychoactive, intoxicating, and addictive properties and the non-psychoactive CBD; CBD can oppose some of the memory and behavioral impairment of THC, CBD does not impair memory as does THC, THC can promote psychotic symptoms, whereas CBD may suppress them; CBD and other cannabinoids also contain potential therapeutic benefits, not as clearly shown with THC, the main psychoactive constituent of marijuana.[4,5,6,7,8,9] Accordingly, their targets, therapeutic indications and benefits are likely to be very different.[10] This compelling evidence supports the need to continue the process and methodologies of modern medicine for the marijuana plant. Since the discovery of its most active chemicals from the 1940's to 1960's, the evolution of marijuana research is following the same principles as those used for nearly two hundred years in developing drug therapies based on botanicals.[11,12] to isolate pure cannabinoids from marijuana and evaluate them individually, to determine whether they have medicinal value, synergistic or opposing effects, at safe and effective doses, through an evidence-based process designed to protect patients and the general public.

The marijuana plant and history of medical use (abbreviated)

Marijuana extracts were listed in the British, and later in the US Pharmacopeia (1850), for sedative and anticonvulsant effects. However, within a century, the British initially, and then the US Pharmacopeia removed marijuana listings (1932, 1941, respectively), as a result of the variable composition of plant preparations, short shelf-life, unpredictable doses, and overshadowing by newer, more targeted, effective pure drugs prescribed at known and reliable doses, with doses that did not elicit overlapping psychoactive and therapeutic reponses.[4] Subsequently, the risks of abuse, intoxication, and other negative consequences of marijuana consumption led to restrictive laws prohibiting the growth, possession and consumption of marijuana. The movement to revive marijuana as a medicine is driven by multiple factors, many beyond the domain of science.[13] One propellant of the movement is the inadequate relief of current approaches to address a number of debilitating chronic diseases or symptoms, including Multiple Sclerosis, Crohn's disease, Parkinson's disease Alzheimer's disease, Amyotrophic Lateral Sclerosis, cancer, seizure disorders, arthritis, spasticity, chronic pain, inflammation, cachexia. These and other medical conditions are frequently cited by proponents of medicinal marijuana.

Troublesome and critical questions persist: is marijuana a safe and effective medicine for one or all of these conditions? for all people of all ages? Before addressing this central question, it is essential to survey endocannabinoid biology and function, as it is the foundation of the ever-expanding claims for marijuana use in numerous medical conditions.

Marijuana chemistry, preparations

1. **Known chemistry of *Marijuana sativa.*** The principal cannabinoids in the marijuana plant include THC, CBD, and cannabinol (CBN). THC is the primary psychoactive compound, with CBD, a minimally psychoactive compound, ranking second. THC is found at higher concentrations than CBD, unless the ratio is deliberately altered by genetic selection. The known chemical composition of *Marijuana 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.[2,14,15] 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.[16,17,18,19] In some marijuana preparations, THC levels have risen to radically higher levels, by concentrating processes that yield levels approaching 80% THC.[20,21] Special strains have also been developed to raise the ratio of THC to CBD, so as to minimize putative THC antagonism by CBD.[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 marijuana quality.[23] Preclinical research has shown that a number of non-psychoactive phytocannabinoids elicit pharmacological responses of therapeutic interest. For example, CBD has putative therapeutic applications for treating psychosis, affective and seizure disorders, inflammation, and neurodegenerative diseases. CBD has a good safety profile in humans. Other plant cannabinoids, such as delta-9-tetrahydrocannabivarin, may also be prove therapeutic for epilepsy or obesity. Other plant cannabinoids, such as delta-9-tetrahydrocannabivarin, may also be prove therapeutic for epilepsy or obesity. [24,25,26]

Dose and dose delivery via different routes (smoking, vaporizers, edibles). Marijuana is consumed by various routes, with the most common route smoking,[27] followed by vaporization, and then by the oral route. Marijuana products may be taken by ingesting edibles, liquids, via sublingual or rectal administration, via transdermal delivery, eye drops, creams and aerosols.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 marijuana cigarette, THC pharmacokinetics and effects vary as a function of the weight of a marijuana cigarette, THC potency in the cigarette, its preparation, the concentration of other cannabinoids, the rate of inhalation, depth and duration of puffs, volume inhaled, extent of breath-holding., and dose titration.[27,28] An extensive comparison of smoke (mainstream and sidestream) generated by igniting marijuana and tobacco cigarettes, showed markedly qualitative similarities in specific compounds (e.g. ammonia, carbon monoxide, among others), and also significant quantitative differences.[29] The presence of known carcinogens and other chemicals in mainstream smoke of marijuana cigarettes and implicated in respiratory diseases, is an important consideration when evaluating the safety and risks associated with marijuana smoking.[30] Lower temperature vaporization of marijuana has been postulated as safer than smoking, as it may deliver fewer high molecular weight components than smoked marijuana.[31] Vaporization reduces the characteristic odor of marijuana smoke, enabling diminished awareness by others. Combined with alcohol, vaporized marijuana yields higher maximum concentrations of blood THC (than without alcohol) possibly explaining why performance is more impaired if marijuana is combined with alcohol.[32,33] Hashish oil, a solvent-extracted liquid is consumed by smoking or inhalation, vaporization or as a food additive.[34] 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 route 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. Smoking multiple marijuana 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 marijuana 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.[35,36,37,38,39] Metabolic elimination of THC is much slower after years of heavy marijuana use and is detectable in blood for 30 days or longer.[40,46,47]

Cannabinoid biology, signaling in brain and body

From an evolutionary perspective the cannabinoid signaling system is ancient, and 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, and (4) mechanisms involved in cell accumulation of specific endocannabinoids.

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 brain, it is the most abundant of the G-protein coupled receptors, and mediates most, if not all the psychoactive effects of THC in marijuana. Its brain distribution is strikingly consistent with the pharmacology of marijuana: 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).[44,45,46,47,48] CB2 receptors are predominant in the periphery, on immune cells, hematopoietic systems and other locales. There is evidence of CB2 receptor expression in brain.[49, 50,51] In the brain, CB2 receptors also modulate the release of chemical signals primarily engaged in immune system functions (cytokines, immune cell migration). CB2 receptors are of considerable interest because THC activation of CB2 does not produce psychoactive effects, as does THC on the CB1 receptor. Accordingly, it is a promising target for therapeutics that may circumvent the adverse effects promulgated by drugs (marijuana or THC) that engender psychoactive effects via CB1 receptors.

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). 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. 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 marijuana and other exogenous cannabinoids, their therapeutic potential and undesirable adverse effects. 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 marijuana use during pregnancy and adolescence, possibly affecting brain structure and function. Endocannabinoids and marijuana-altered endocannabinoid signaling may contribute to neuropsychiatric diseases of developmental origins and in which modifications to signaling have been observed: autism, schizophrenia, bipolar disorder and depression. 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[53] and CBD[54] inhibit neurogenesis in adolescent or adult rodent brain, a process of potential relevance to a wide range of marijuana-induced adverse events. 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[55], with CB2 agonists providing anti-inflammatory

protection and CB1 activation promoting hypothermia. The use of marijuana for this purpose is compromised by psychoactive effects and the development of tolerance to its neuroprotective effects. The endocannabinoid system contributes to olfactory, auditory and pain sensations. A review of these other functions is beyond the scope of this summary but readers are referred to an excellent overview.[56] 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. 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.[57] Endogenous and exogenous cannabinoids, including marijuana and THC affect sleep patterns and promote sleep. The endocannabinoid system has mood elevating, anti-depressant and anxiolytic effects. The anxiolytic response to marijuana is biphasic, implying that marijuana dosing is a critical factor in minimizing risk of anxiety, depression and maximizing benefit.[58,59,60] Yet, marijuana at high doses, possibly by down-regulating CB1 receptors, increases the risk for depression or anxiety. The endogenous cannabinoid system inhibits seizure susceptibility. Marijuana has antiseizure activity. However, if the dose of THC is high or marijuana is consumed by susceptible individuals, THC may promote seizures. CBD has therapeutic potential as antiepileptic drug without the psychoactive effects, or potential for pro-seizure activity of whole plant marijuana.[61,62] 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.[63] 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.[64] 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.[65,66,67] THC and marijuana decrease working memory, apparently by actions in the hippocampus, a brain region critical for learning and memory. The memory decrements induced by THC or marijuana resemble hippocampal lesions. These impairments may result from suppression of glutamate release in the hippocampus, which is responsible for the establishment of synaptic plasticity.

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.[68] Differences in CB1 and CB2 receptor function in the body is a focus of this segment, because THC in the marijuana plant activates both CB1 and CB2 receptors and could have detrimental effects in tissues in whichCB1 receptor activity may contribute to pathophysiological states. 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). Virtually all gut functions are regulated by endocannabinoids, critical for CNS control of its metabolic and homeostatic functions. 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 marijuana is mild tachycardia, with increases in cardiac output and increased myocardial oxygen requirement. Case reports of cardiovascular side effects of THC/marijuana have been reported and it is essential to proceed cautiously with marijuana and other cannabinoids in susceptible individuals. 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 the cardiovascular complications of liver disease. In

contrast, CB2 is protective, reducing these indices of liver dysfunction. Endocannabinoids modulate the functional activities of immune cells, largely though CB2 receptors, providing novel targets for therapeutic manipulation. Endocannabinoid signaling (largely through CB2 receptors) contributes to regulating energy metabolism in muscle and the formation of new muscle fibers. 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.

Marijuana toxicity in humans

The primary risks of using marijuana have been discovered by investigating users of marijuana for recreational purposes. Few studies have reported on long term consequences of marijuana if used for medical purposes, although there may be few differences in response in the two cohorts as the therapeutic and psychoactive doses overlap extensively. Marijuana engenders acute pharmacological effects, longer term health risks for the brain, body and behavior, and public safety concerns. These effects are summarized in a recent report by the World Health Organization.[69] Topics include acute and persistent effects of marijuana on cognitive function, on recently abstinent marijuana users, on persistent effects one month after last use. [70,71,7273,74,75] Other effects, especially relevant to adolescents, include the association of marijuana with psychosis and schizophrenia, and effects during development, [76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93, 94,95, 96, 97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114] risks for using other drugs.[115,116,117,118,119] Marijuana impairs driving ability and confers a higher risk for motor vehicle accidents, and workplace disruptions.[120,121.122,123] Marijuana use is associated with an increased risk for cognitive decline, psychosocial impairment, vehicle crashes, emergency department visits, psychiatric symptoms, poor quality of life, educational and employment achievement, use of other drugs, adverse health effects, and fetal development.[124,125,126]

Marijuana Use Disorder

Marijuana is the most widely used illicit substance in the world.[127] There is strong scientific support for concluding that marijuana has high potential for abuse, is actually abused and is addictive, particularly in youth with other consequences (e.g. psychosis) related to age on onset, marijuana potency and frequency of use .[128,129,130,131,132,133,134,135]

Marijuana as a medicine for symptom relief, for treatment of disorders/diseases

1. **Overview of safety, efficacy standards.** Several countries (Canada, Netherlands, Israel) and 24 of 50 states in the United States have approved the use of marijuana for medicinal purposes, with or without undergoing a systematic medicines approval process. In this review of the current status of marijuana as a medicine, a simple question is addressed: are clinical trials that report marijuana-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 has 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. If effective and safe medical applications emerge for phytocannabinoids, synthetic cannabinoids or metabolic modulators, the scientific process is not a barrier to their approval.

2. Marijuana chemistry and route of administration. The two main cannabinoids in marijuana, THC and CBD are instructive. A safe therapeutic window for marijuana has not been established, and clinical trials (see below) have used THC from 1%-23% (a 23-fold dose range). If it is ineffective at low doses, how high can THC levels be driven before susceptible users experience intense and severe psychological or neurological symptoms such as anxiety, psychosis and seizures?[136,137] The same marijuana plant contains another cannabinoid that can oppose the adverse effects of THC.[138] Even though CBD levels are declining, CBD reduces anxiety, may function as an anti-psychotic and anti-convulsant.[139,140] Yet, the ratio of THC to CBD has been rising in the marijuana plant, even though this shift may result in more adverse mental health consequences among users, even though this shift may result in more adverse mental health consequences among users. The therapeutic potential of CBD, the non-psychoactive constituent of the marijuana plant, is currently under investigation in 20 ongoing or planned clinical trials. These include treatment of psychosis, inflammatory bowel disease, seizure disorders, addiction, and as an immunosuppressant. [141]

3. Entourage effect.[142] A widely held and user-reported *belief* is that the benefit of whole plant marijuana provides more relief than isolated cannabinoids, the "entourage effect. This is not a trivial issue, as it is a motivating force for whole plant medicinal marijuana in lieu of isolated compounds. Conceivably, at least four explanations may contribute to these self-reports: (1) as noted above, CBD may ease THC-induced anxiety or psychosis; (2) pharmacokinetics may account for these perceived differences. Side-by-side comparisons with the two preparations can clarify this claim. Yet, a clinical trial comparing the effects of smoked marijuana with dronabinol (THC alone) suggested that, under controlled conditions, marijuana and dronabinol decreased pain, but dronabinol produced longer-lasting decreases in pain sensitivity and lower ratings of abuse-related subjective effects than marijuana[143]. In another pilot study, caloric intake and body weight were measured in HIV-positive marijuana smokers, and compared with placebo or dronabinol. Marijuana and dronabinol effects were comparable, with both dronabinol and marijuana well-tolerated and producing substantial and comparable increases in food intake.[144] All cannabinoid conditions produced significant intoxication, except for low-dose dronabinol. No other clinical trials have compared smoked marijuana to oral/spray THC or THC/CBD for other medical conditions, leaving the issue of whether smoked marijuana confers an advantage in efficacy and safety unresolved. Randomized Clinical trials comparing smoked marijuana with alternative medications are scant. (3) Marijuana users prefer inhalation because swift brain entry conceivably produces rapid euphoria. Yet most medications that provide symptom relief are delivered orally. (4) Cannabinoids are not the only products of the marijuana plant with putative medicinal properties. Marijuana terpenoids share a precursor to cannabinoids, e.g. limonene, myrcene, α-pinene, linalool, and some 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 marijuana is superior to isolated compounds because of synergism between various components.

It is generally recognized that smoking can be harmful to health.[145] Standard medicines are not smoked, but enter the body by other routes (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 marijuana, the percent of THC that enters the body is variable depending on the type of smoking ritual or route of administration.[146,147,148] 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 marijuana smokers.[149] Nearly all cross-sectional and

longitudinal studies evaluating marijuana 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), but not with shortness of breath or lung cancer, but possible cancer risks remaining for heavy smokers.[150,151] Whether vaping is a safer alternative to smoking marijuana 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 marijuana showed modest relief of neuropathic pain in 39 and 8 patients,[152,153] with one at a very low dose of THC (1.29%). In support of this method of delivery, vaporized or smoked marijuana yielded similar maximal, but a *wide range of inter-subject blood levels* of THC. 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.[154]

4. Missing safety data. Isolated cannabinoids have undergone a number of randomized, controlled clinical trials documenting safety, efficacy and side effect profiles, as required in a formalized drug approval process, whereas few RCT are reported for whole plant marijuana. In the absence of long term clinical trials, most data by necessity is extrapolated from recreational users. We failed to identify clinical trials of long duration that investigate outcomes in people using marijuana long-term for chronic medical conditions, even though marijuana 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 marijuana users develop an addiction to marijuana. 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 marijuana can be safely used under medical supervision, for long term open-ended use. This segment provides guidance on the quality of existing clinical trials and a roadmap for future research. Key information about side-effects and safety would be collected if marijuana went through the normal evaluation process for approval as a medicine. Of randomized controlled trials, the majority of trials do not report a full dose-response evaluation, inclusion criteria generally require subjects to be experienced marijuana 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).

5. Missing Safety data. Cognitive impairment in medical conditions with cognitive decline. Side effects of marijuana have to be viewed in the context of immediate effects and after repeated long term use. In research of subjects under the influence of marijuana, 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 marijuana 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.[155] Regular marijuana use for medicinal purposes is so recent 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). For example, cancer or chemotherapy promote cognitive decline before, during or after chemotherapy, with memory loss, loss of concentration and attention the most frequent symptoms.[156,157] Conceivably, the combination of chemotherapy and marijuana reduces cognitive functions in additive or synergistic ways. Yet the impact of marijuana on parameters of cognition has not been tested, although the number of patients using marijuana during chemotherapy is growing. For multiple

sclerosis, another disease beleaguered by cognitive impairment, it is now recognized that marijuana worsens cognitive deficits.[158] Reports on marijuana-induced relief of physical symptoms in other neurodegenerative disorders with cognitive impairment (Parkinson's disease, Alzheimer's disease), do not judiciously measure cognition. Marijuana may compromise quality-of-life for these populations but this parameter remains inadequately explored.

6. Long term effects. A significant number of individuals report paranoia, persecutory ideas, or hallucinations while under the influence of marijuana[159] and with drug-naïve study subjects, high drop–out rates would compromise the integrity of the clinical trial. Considering the concerted effort during the 20th century to minimize or eliminate psychoactive effects of any medication, clinical trials should include side-by-side comparisons of marijuana with isolated cannabinoids or alternative drugs (e.g. for chemotherapy-induced nausea, pain, or glaucoma). 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. Marijuana can reduce motor coordination alone, or combined with alcohol, slow the reaction time of drivers[160]. Marijuana 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[161]. 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.

7. Evidence of Marijuana for Medicinal Use: Use of marijuana by individuals, internationally. A recent, international survey of 31 countries investigated self-reported medicinal use of marijuana (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%). Marijuana 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%).[162] With the exception of multiple sclerosis, and neuropathic pain, randomized controlled trials (RCT) with marijuana 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 marijuana, as corroborated by surveys, case-based studies, anecdotal self-reports, laboratory-based short-term trials. Nonetheless, rigorous criteria need to be applied as would be required by the FDA, EMA or WHO, using the gold standard of RCTs for the drug approval process. Evidence from RCTs is presented, with sources from primary manuscripts and 10 meta-analyses.[163,164] The psychoactive responses engendered by marijuana 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 marijuana-using populations.[165] The majority of RCT trials recruit experienced marijuana using subjects for a number of reasons, including concerns of unacceptably high drop-out rates among marijuana-naïve subjects.[166]

8. Neurological diseases or symptoms. Several recent reviews and meta-analyses have weighed in on the therapeutic indications for neurological diseases.[167,168,169,170] 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 marijuana is to compromise cognition. This effect needs to be considered in weighing the risks-benefits of marijuana.

Multiple Sclerosis. Multiple sclerosis (MS) is an inflammatory, autoimmune, degenerative disease of the central nervous system.[171] It is among the most common causes of non-traumatic neurological disability in young adults of northern European descent.[172.173] Globally it affects about 2–3 million people,[174] 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.[175,176] Approximately 14–18% of MS patients use marijuana for symptom relief from pain, spasticity and insomnia.[177] Given that cognitive impairment occurs in approximately 40–60% of patients with multiple sclerosis, is associated with structural and functional brain changes,[178,179] and given the effects of MS on cognition, patients who smoke marijuana may be particularly vulnerable to cognitive deficits and brain changes attributed to marijuana. MS patients who smoke marijuana display additional deterioration in measures of cognition, including processing speed, memory, executive functioning, and deficits in recruiting brain regions during a memory task.[180,181,182] Furthermore, marijuana 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 marijuana-using MS population compared the non-marijuana MS group. This association between marijuana use, cognitive impairment and structural brain changes in MS patients[183] is a cautionary example of the multiple factors to consider along with the therapeutic potential of marijuana.

There is some evidence that the endocannabinoid system is dysregulated in MS.[184] In an animal model of MS, the neurodegeneration rate can be reduced by administration of CB2 agonists, exogenous 2-AG administration, or elimination of the major degrading enzyme FAAH, in transgenic mice.[185,186,187] 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,[188,189] but evidence that cannabinoids can function as neuroprotective agents is weak, as THC failed to attenuate MS progression or disability.[190] MS is characterized by a wide range of cognitive and physical symptoms; clinical trials with marijuana need to consider whether marijuana improves or compromises a range of symptoms, including cognition, simultaneously and whether the costs outweigh the benefits of treatment.[191]

We identified three RCT using inhaled or vaporized marijuana to treat MS symptoms.

1. A double-blind randomized placebo-controlled study of inhaled marijuana smoke on postural responses was performed in 10 adult patients (5 female, 5 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 marijuana 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 is that marijuana smoking worsens posture and balance in MS patients.[192]

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 marijuana (4% THC), once daily for three days, or control identical placebo cigarettes, once daily for three days.[193] 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 marijuana users, and 30 completed the trial. Seven subjects dropped out of the study, the majority marijuana-naïve. Treatment with smoked marijuana 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%) neausea (11%), too "high" (6%) were reported side effects. Authors concluded that smoked marijuana was superior to placebo in spasticity and pain reduction in participants.
Another RCT may reside on the "margins" of this review, because oral THC was compared with an oral "marijuana 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 marijuana containing its constituents.[194] This randomized, double-blind, placebo-controlled, twofold crossover study was conducted in 16 patients with MS for 4 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. In summary, there is insufficient evidence to support the use of smoked marijuana for MS. These conclusions are similar to those drawn by analysis and meta-analyses of the biomedical literature in recent reviews.[195,196,197]

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. HIV-infected individuals report improvements in health from smoking marijuana. Of over 200 people with HIV-AIDS, 23% used marijuana in the previous month.[198].[199] The association between marijuana use for psychoactive purposes and marijuana used medically for HIV-AIDS is relevant, [200] with considerations including Both marijuana use and duration of HIV infection may affect cognitive functioning that may impair their ability to follow important treatment guidance.[201,202] While evidence for an effect of inhaled marijuana 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 marijuana users are relevant to an overall cost-benefit analysis of long term marijuana use to treat chronic neuropathic pain.

Six recent manuscripts reporting randomized controlled clinical trials with marijuanasmoked or vaporized marijuana. Five were recently summarized positively in a review co-authored by investigators of the primary studies.[203] 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 marijuana and cannabinoids for pain.[204,205] These RCT are currently insufficient and inadequate to recommend use of marijuana (smoked or vaporized) for the treatment of neuropathic pain.No RCT are reported for ingested marijuana, which displays variable onset times, inability to titrate doses, and more side effects.

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 marijuana.[206]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.

HIV-associated sensory neuropathy (3.5% THC). This study measured the effect of smoked marijuana on neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model.[207] 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 marijuana 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 marijuana 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.

Neuropathy: low to moderate doses (1.29%, 3.53% THC). Wilsey et al[208] conducted a similar study with smoked marijuana and then followed up in a larger cohort, assessing vaporized marijuana in a broader range of neuropathies with two doses of THC (1.29% and 3.53%) compared with placebo.[209] Both active study medications provided statistically significant 30% reductions in pain intensity, comparable to 2 commonly used anticonvulsants used for neuropathic apin treatment. Psychomotor tasks revealed significant marijuana impairment at 60 minutes and at 4 hours, with performance worse at the higher THC dose. The author concluded that marijuana 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 marijuana users become tolerant to marijuana-related performance-impairing effects, more recent comparisons of marijuana-related effects on cognitive performance of frequent users suggest impairment on a variety of cognitive tasks, which may be dose and age-dependent.[210] Undesirable consequences of smoking marijuana may be acceptable to pain patients,[211] but in the absence of evidence, and high drop-out rates of the few marijuana-naïve subjects in these studies, this indication for medicinal use of marijuana remains unresolved.

HIV-AIDS neuropathy (1%-8% THC). Ellis et al[212] also assessed smoked marijuana for HIV-AIDS neuropathy in a cross-over design. Among 28 completers (27 experienced marijuana users), pain relief was greater with marijuana than placebo, with 46% achieving at least 30% pain relief with marijuana versus placebo (18%). Most side effects were mild and self-limited, but 2 subjects experienced treatment-limiting toxicities. Smoked marijuana 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.

Neuropathy (2.5 - 9.4% THC). Ware et al[213] tested three doses of smoked marijuana for chronic neuropathic pain (2.5%, 6%, 9.4% THC) in which 18/24 were experienced marijuana 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 marijuana in a cohort of eight patients with chronic neuropathic pain on a stable analgesic regimen including marijuana.[214] 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.

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. 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 RCT with whole plant marijuana to treat symptoms of Alzheimer's disease or progression of the disease and no strong evidence that marijuana alleviates symptoms.[215] Some intriguing positive benefits relevant to the degenerative process are derived from cellular or imperfect animal models.[216] Four randomized trials 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).

Other Neurological Conditions: Epilepsy. There are no reported RCT with marijuana use in any form of epilepsy.[217] **Huntington Disease Dyskinesias:** There are no RCT with marijuana for this condition. **Parkinson's disease (levodopa-induced dyskinesias):** There are no RCT with marijuana for this condition and marijuana is not recommended for treatment.[218] A recent an open label trial reportedly found positive improvements in Parkinson's diseased patients that smoked marijuana.[219] Others recommend more research with isolated cannabinoids.[220] **Cervical Dystonia:** There are no RCT with marijuana for this condition**. Tics Of Tourette Syndrome:** There are no RCT with marijuana for this condition. **Summary.** Marijuana reduces neuropathic pain in a sub-population of experimental subjects, in very short term clinical trials. Beyond the setting of a clinical trial, adverse events, particularly cognitive impairment are a significant concern with marijuana use.

9. AIDS Wasting, Cachexia and Appetite Enhancement. Studies have shown that smoked or ingested marijuana, 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 marijuana or individual cannabinoids of short duration (21 - 84 days) were identified for the treatment of AIDS in a small number of patients[221]. Other measured changes included viral load, weight, body fat, appetite, caloric intake nausea and vomiting, performance and mood. **AIDS viral load.** Marijuana (3.95%) or dronabinol or placebo had no adverse effect on viral load or protease inhibitor pharmacokinetics.[222] Smoked and oral cannabinoids appeared safe in people with HIV infection in the short duration of the study, 21-days. **AIDS and appetite.** Appetite enhancement is indicated in diseases characterized by loss of appetite and wasting. Tolerability and efficacy of smoked marijuana (1.8%; 2.8%; 3.9% THC) and oral dronabinol in HIV-positive marijuana smokers was compared in those with and without a clinically significant loss of muscle mass, component of AIDS wasting. Marijuana and the lower dronabinol doses (10, 20 mg) were well tolerated (e.g., few physical symptoms, significant increases in ratings of "good drug effect") in both groups of participants. Marijuana and dronabinol significantly increased caloric intake in the low bioelectrical impedance analysis (BIA) group but not in the normal BIA group. 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 marijuana at home throughout the study (no regulated doses), with marijuana prohibited on the morning of testing. For experienced marijuana smokers with clinically significant muscle mass loss, both dronabinol and marijuana produce substantial and comparable increases in food intake without producing adverse effects.[223] These findings question the need for a smoked product if an FDA-approved drug is equally effective. **HIV-AIDS and appetite, mood, cognitive performance, physiologic measures, sleep.** A placebo-controlled within-subject design evaluated marijuana and dronabinol across a range of behaviors: HIV-positive marijuana smokers (n = 10) completed two, 16-day inpatient phases.[224] Each dronabinol (5 and 10 mg) and marijuana (2.0%, 3.9% THC) dose was administered 4 times daily for 4 days. Compared with placebo, marijuana and dronabinol dose dependently

increased daily caloric intake and body weight in HIV-positive marijuana 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 marijuana and dronabinol were comparable, except that only marijuana (3.9% THC) improved ratings of sleep. These data suggest that for HIV-positive marijuana smokers, both dronabinol (at doses 8 times current recommendations, likely because of tolerance due to prior heavy marijuana use), and marijuana produced substantial and comparable increases in food intake. A sustained effect of marijuana on AIDS-related morbidity, mortality, safety in patients on effective antiretroviral therapy has not been shown. The available evidence is insufficient or low quality[225] to alter medical and regulatory guidance.

10. Cancer, Symptom Management (nausea, vomiting, appetite, pain): Marijuana has been proposed to alleviate symptoms of cancer, including reduced appetite, chemotherapy-induced nausea and vomiting, cancer pain and even to attenuate the disease process. **Cancer, Chemotherapy and anti-emesis.** Chemotherapy-induced nausea and vomiting were inadequately controlled in the 1960's and 1970's, motivating investigation of the anti-emetic properties of cannabinoids and leading to FDA approval of nabilone and THC (dronabinol or Marinol). There have been only three small clinical trials on the use of marijuana in cancer patients.[226] 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. Consequently, there are insufficient data to provide an overall level of evidence for the use of marijuana for chemotherapy-induced nausea and vomiting. There are no published data on the use of marijuana for other cancer-related or cancer treatment–related symptoms.[227]

Yet some patients prefer smoked marijuana over oral cannabinoids, with rationales that include ability to self-titrate smoked marijuana, the swallowing of pills is difficult while experiencing emesis, onset of relief is faster with smoking, and the whole plant ("entourage") is more effective.[228] Side-by-side clinical trials with oral cannabinoid compared with smoked marijuana in HIV-AIDS (see above) show scant evidence for therapeutic advantage of smoked marijuana. 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 marijuana engenders a higher rate of brain entry and associated undesirable side effects, which can include intoxication, anxiety, acute psychotic reactions, and orthostatic hypotension.[229] It is questionable whether the beneficial effects of inhaled marijuana outweigh the risks. 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.[230] A significant proportion of older cancer patients with no previous marijuana experience refused to continue its use because they found the psychoactive effects too unpleasant. For such reasons, there is doubt whether smoked marijuana will find widespread clinical application, except among those who have previously used it for nonmedical purposes.[231] Paradoxically cannabinoids can be both anti-emetic and pro-emetic. A cannabinoid hyperemesis syndrome has recently been described, in which persistent and regular marijuana use (i.e., daily or weekly use for more than 1 year) is associated with episodic nausea and vomiting[232] and nonresponse to treatment for cyclic vomiting other than hot showers.[233]

Marijuana, symptoms and anti-tumor activity. At present, there is insufficient evidence to recommend inhaling marijuana as a treatment for cancer-related symptoms or cancer treatment–

related side effects.[234] There is no credible evidence that smoked marijuana is an anti-tumor agent.[235] In fact data show contradictory results. 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 steps are insufficient to satisfy stringent criteria for recommending marijuana to treat 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,[236] THC did not extend the life span of these patients.

11. Crohn's Disease. There is evidence that marijuana use is higher in patients with inflammatory bowel diseases[237], but until recently, these reports were not subjected to controlled trials. In a prospective trial to determine whether marijuana can induce remission, 21 marijuana-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 marijuana cigarettes (THC, 23%; less than 5% CBD) twice daily or placebo marijuana with THC extracted, for 8 weeks of treatment and 2 weeks thereafter. Complete remission was achieved in 5 of 11 subjects in the marijuana group (45%) and 1 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 marijuana group 4 of 10 in the placebo group. Three patients in the marijuana group were weaned from steroid dependency and Marijuana 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 marijuana group rebounded to pretreatment levels, and at 10 weeks, there was no difference in mean rating scale results between the placebo and marijuana groups. The authors concluded that marijuana use produced a significant, clinical, steroid-free benefit in patients with active Crohn's disease even though 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 marijuana produced significant clinical, steroid-free benefits to 10 of 11 patients with active Crohn's disease, compared with placebo, without side effects[238]. Intriguingly, there was no difference between study 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 marijuana 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. Marijuana may conceivably reduce inflammation indirectly by reducing stress, but symptomatic improvement without a reduction in inflammation could cause ongoing intestinal structural damage. Before marijuana can be recommended for the treatment of Crohn's disease further larger studies are required as the small sample size in the treatment group did not provide sufficient evidence to change clinical practice.

12. Post-traumatic stress disorder (PTSD) or sleep disorders. There are no large scale randomized controlled trials with marijuana to alleviate PTSD symptoms. On the contrary, marijuana use may impede the effectiveness of treatment for PTSD, and is associated with poorer clinical outcomes with PTSD. [239],[240]

13. Glaucoma. Glaucoma is an array of ocular disorders which leads to visual deficits or blindness[241]. Elevated intraocular pressure (IOP) is a primary cause of vision loss. Marijuana lowers blood pressure and may also reduce aqueous humor production via cannabinoid receptor activation, pharmacological actions that temporarily reduce IOP.[242,243,244] 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

marijuana 6 to 8 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[245]. Another challenge to using marijuana is the development of tolerance to its pharmacological actions in the eye[246], 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 marijuana[247]. Cannabinoids failed to reduce IOP in glaucoma patients in a small clinical trial[248].

Summary

1. The chemical composition of marijuana and its various preparations (smoke, vapor, edibles, beverages, creams, suppositories, etc) is variable; safe and effective dose ranges (and plant strain) for each medical condition remain uncertain, unresolved.
2. Efficacy criteria have not been fulfilled by rigorous research.
3. Side-by-side studies comparing currently approved, and possibly safer medications are rare. Similar unknowns exist for opioids.
4. Safety studies are inadequate and of short duration; a growing body of scientific evidence shows that marijuana use for psychoactive purposes is unsafe and associated with unhealthy outcomes. Long term studies on use of various forms of dispensary marijuana for medicinal purposes are not widely available. Similar unknowns exist for opioids.
5. There is no consensus by qualified experts that marijuana is a medicine.
6. Raw data are not available for a number of clinical reports.

The 1999 Institute of Medicine report summarized the status of marijuana plant by concluding that, "if there is any future in marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives."

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