Update of Cannabis and its medical use

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Contents

Preface 3
Terminology.....

form of brain delivery considered a route of administration

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

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 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

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 rece

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

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

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]

cannabis.[172,173,174,175]

addicted cannabis users unmasks physical neuroadaptation, manifested by physical, significant discomfort

(3) Cannabinoids are not the only products of the cannabis plant with putative medicinal properties. Cannabis terpenoids share a precursor to cannabinoids (-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 1 09 Tm

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, 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

It should be noted that t

1. A double-blind randomized placebo-

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 iieduct.963liip r(er)8(er)-5(e)-32(i)-41( )-238

aiQan(o)11(r)-5 Favntag ofneuropaabwitiNdoses of THCe 1 108(30)11(i)16[(a)-12(t)5(o)11( )] TJETBT1 0 0 1 725454 583.54 3.33%g)g

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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). I

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