REVIEW ARTICLE
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Adverse Effects of Recreational and Medical Cannabis

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ABSTRACT ~ ***Purpose of Review:*** *This comprehensive review discusses the adverse effects known today about marijuana, for either medical or recreational use. It reviews the role of cannabis in the treatment of chronic pain, cognitive and neurological adverse effects, special cases and addiction.* ***Recent Findings:*** *Cannabinoids work through the endocannabinoids system and inhibit the release of GABA and glutamate in the brain, impact neuromodulation, as well as dopamine, acetylcholine and norepinephrine release. They affect reward, learning and pain. The use of cannabis is increasing nationally and worldwide for both recreational and medicinal purposes, however, there is relatively only low quality evidence to the efficacy and adverse effects of this. Cannabis and its derivatives may be used for treatment of chronic pain. They are via CB1 receptors that are thought to modulate nociceptive signals in the brain. CB2 receptors in the DRG likely affect pain integration in the afferent pathways, and peripherally CB2 also affects noradrenergic pathways influencing pain. A large proportion of users may see more than 50% of chronic pain alleviation compared with placebo. Cannabis affects cognition, most notably executive function, memory and attention, and may deteriorate the boundary between emotional and executive processing. Cannabis impairs memory in the short run, which become more significant with chronic use, and may also be accompanied by poorer effort, slower processing and impacted attention. It is generally believed that long-term use and earlier age are risk factor for neurocognitive deficits; neuroimaging studies have shown reduced hippocampal volume and density. Executive functions and memory are worse in adolescent users versus adults. Cannabis addiction is different and likely less common than other addictive substances, but up to 10% of users meet criteria for lifetime cannabis dependence.*

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Addiction patterns may be linked to genetic and epigenetic differences. It is still unclear whether abstinence reverses patterns of addiction, and more research is required into this topic. ***Summary:*** *Cannabis use has become more abundant for both medical and recreational use. It carries likely benefits in the form of analgesia, anti-emesis and improved appetite in chronic patients. The evidence reviewing adverse effects of this use are still limited, however, exiting data points to a clear link with neurocognitive deterioration, backed by loss of brain volume and density. Addiction is likely complex and variable, and no good data exists to support treatment at this point. It is becoming clear that use in earlier ages carries a higher risk for long-term deficits. As with any other drug, these risks should be considered alongside benefits prior to a decision on cannabis use.* Psychopharmacology Bulletin. *2021;51(1):94–109.*

Introduction

Cannabis is a genus of flowering plant whose most well-known species include *sativa*, *indica*, and *ruderalis*.[1] In its dried flower bud form it is referred to as marijuana.[1] Blocks of its plant resin are known as hashish.[1] Flavonoids, cannabinol, terpenoids, and cannabinoids are some of the bioactive molecules that dictate the qualities of different cannabis strains.[1,2] The relative proportions of cannabinoid varieties in a given strain determine psychoactive potency.[1] Of the nearly 100 types of cannabinoids, the two most well-known and clinically relevant are delta-9-tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, and cannabidiol (CBD), an anti-inflammatory agent.[1] THC is a partial agonist of cannabinoid receptor 1 (CB1 receptor) while CBD is a CB1 receptor negative allosteric modulator.[3]

The mechanism of action by which cannabinoids exert their effects involves binding to G protein-coupled CB1 and CB2 receptors throughout the body, stimulating the endogenous cannabinoid system, altering levels of endocannabinoids (eCBs), and inhibiting release of neurotransmitters like gamma-aminobutyric acid (GABA) and glutamate.[1,2] CB1 and CB2 receptors also allow for other forms of neuromodulation, including increased dopamine release, decreased acetylcholine release, and decreased norepinephrine release.[4] eCBs are endogenous neuroactive lipid messengers that play a role in reward, memory, learning, and pain pathways.[1] The highest concentrations of CB1 and CB2 receptors are found in the central nervous system and in immune cells, respectively.[1]

Societal and legal perceptions of cannabis have been shifting over the recent years. Cannabis underwent national legalization in Canada in October 2018 and is experiencing a trend toward legalization in the United States.[5] In 2017, it was estimated that 43% of individuals ages 16–24 and 18% of individuals over 25 used cannabis in Canada.[5] Nationwide use of cannabis in the United States has increased from

5.8% of people age 12 or older in 2007 to 7.5% in 2013.[6] From what has been observed in Canada and in parts of the United States like Colorado and Washington, it is thought that with legalization comes increased acceptance, reduced perception of risk, and increased use of cannabis by both adults and adolescents.[5] These anticipated trends make it essential to improving current understanding of both the basic science and clinical applications of cannabis.[5]

Medical cannabis is becoming more frequently encountered in the medical records of patients with chronic pain. This worldwide surge is illustrated in part by the statistic that 40% of cancer patients use cannabis for pain management in places where access to medical cannabis is legal such as Canada, Germany, and Israel.[7] Despite the fact that medical cannabis and cannabis-based medicines (CBMs) such as dronabinol and nabiximols have been made available for pain management in an increasing number of countries, the amount and quality of evidence for the use of these agents is low.[7]

Unfortunately, the opportunity to carry out optimally designed randomized controlled trials for cannabis is limited by the ideal that clinical exposure to a potentially harmful substance like cannabis is unethical.[8] Further, regulatory barriers, supply barriers, and funding limitations make it difficult to research cannabis. The majority of cannabis used for clinical research in the United States has long been supplied by the University of Mississippi and overseen by the Drug Enforcement Administration (DEA).[9] Albeit streamlined and seemingly well-controlled, research is thus being conducted on a federally-regulated cannabis supply that does not reflect the products that being used by consumers.[9] Thus, in addition to recall bias and underpowered sample sizes, studies of cannabis are also generally limited in external validity.

Cannabis and its Role in the Treatment of Chronic Pain

It is estimated that the prevalence of chronic pain is 6%–10%.[10] Given that chronic pain often has neuropathic components, many pharmacological treatments currently offered to patients who complain of chronic pain target nerve pain.[10] Unfortunately, many treatment options for neuropathic pain have unfavorable adverse effect profiles.[10] These circumstances beg for further exploration of new treatment options, especially those that may implement unconventional mechanisms of action. Cannabis has been used for millennia for the homeopathic reduction of pain and with increased availability by way of legalization, patients are increasingly inquiring about its use for the treatment of chronic pain in various medical settings.[10]

Cannabinoids may be extracted from their natural plant source and ingested in herbal form or manufactured synthetically.[1] While production of medical cannabis is not yet widespread in the United States due to currrent federal regulations, various forms of medical cannabis are available in other parts of the world.[1] Nabiximols (Sativex, GW Pharmaceuticals, UK) is an oromucosal spray that contains a 1:1 mixture of THC and CBD isolated directly from *Cannabis sativa*.[1] Dronabinol capsules (Marinol, Banner Pharmacaps Inc., USA), nabilone (Cesamet, Valeant Pharmaceuticals International, Canada), and generic THC in oral or inhaled solutions are synthetic forms of cannabis used for treatment of chronic pain.[1]

CB1 receptors are densely populated in the hippocampus, association cortices, cerebellum, and basal ganglia.[1] These receptors are notability similar in neurochemical structure to opioid receptors, and are thought to modulate nociceptive processing in the brain.[1] CB2 receptors are found in high concentration in the dorsal root ganglion sensory neurons and in the spinal cord, areas that are known sites of intense nociceptive integration.[1] CB2 receptors that are involved in the release of analgesic beta-endorphins have been shown to reduce C-fiber activity in neuropathic pain models.[1] It has been demonstrated that outside of the central nervous system, peripheral cannabinoid receptors are involved in anti-nociception via the activation of noradrenergic pathways.[1]

A Cochrane review conducted in November 2017 considered randomized, double-blind controlled trials of medical cannabis—defined as herbal cannabis or plant-derived and synthetic cannabis-based medicines—versus placebo or any other active treatment for chronic neuropathic pain.[10] Published and ongoing trials were found using a literature search of CENTRAL, MEDLINE, Embase, and two unspecified trials registries.[10] The review analyzed data from 16 studies with 1750 participants to evaluate medical cannabis for efficacy, tolerability, and safety.[10] The forms of medical cannabis were the oromucosal spray, nabilone, inhaled herbal cannabis, and dronabinol.[10] One study compared medical cannabis against dihydrocodeine instead of placebo.[10] The review used the Cochrane 'Risk of Bias' tool and GRADE to assess the quality of data, determining that overall study quality was very low to moderate given the prevalence of moderate bias judgments and moderate study quality.[10] Of note, none of the evidence qualified as high-quality using the assessment criteria.[10]

According to the Cochrane review, it was determined that medical cannabis may increase the number of people achieving 50% or greater pain relief compared with placebo.[10] It was noted that Patient Global Impression of Change was very low quality and that while tolerability between herbal cannabis and placebo did not differ, more patients with-

drew from studies due to adverse effects of medical cannabis compared to placebo.[10] There was not enough evidence to conclude if medical cannabis directly increased the frequency of serious adverse events compared to placebo.[10] In the analysis of secondary outcomes, it was determined that medical cannabis may increase nervous system adverse effects and that psychiatric disorders are more likely to occur with patients using medical cannabis than placebo.[10] No conclusions were made about long-term risks.[10] The authors concluded that the potential benefits of medical cannabis in the treatment of chronic pain may be outweighed by potential adverse effects.[10] The evidence supporting the efficacy of cannabis for treatment of chronic pain is limited by small sample sizes and strict exclusion criteria that limit external validity for patients with significant comorbidities or history of substance abuse.[10]

An important subset of patients with chronic pain are those with oncologic conditions. In patients with advanced cancer, the prevalence of pain is estimated to be 70%.[7] In most cases, cancer pain is defined as pain arising as a direct consequence of the disease and not due to therapy or the presence of a comorbid condition.[7] According to the World Health Organization, opioids are an appropriate first-line treatment for moderate-to-severe cancer pain.[7] Considering the widespread use of opioids in the treatment of oncologic pain, there has been a specific focus in investigating the utility of medical cannabis for treatment of pain both as an alternative to opioids and as a therapeutic adjunct to decrease opioid doses.[1] A meta-analysis of two studies found a trend toward greater pain reduction with cannabinoids compared to placebo, but these results are tagged by low quality of evidence.[11] It has been shown that high doses of THC are significantly superior to placebo in pain reduction and moreover comparable to codeine.[1] Like opioids, high doses of THC are associated with significant sedation.[1] In trials of combination THC/CBD preparations in subjects with oncologic pain refractory to opioids, patients endorsed analgesia with low to medium dose nabiximols compared to placebo.[1] Patients treated with high dose nabiximols experienced poor drug tolerability.[1] Interestingly, a comparison of the efficacy of THC/CBD to THC alone and to placebo showed that the combination of THC/CBD had superior pain relief that was sustained for as long as two years without the need of increasing opioid regimens.[1] An observational study of patient-reported cancer-related symptoms treated with cannabis found a similar pain lessening effect but also noted a reduction in opioid dose in close to half of the subjects.[1]

While these results are promising, they are difficult to generalize given inconsistency of cannabis preparations and dosages used by and prescribed to patients.[1] At present, studies reporting positive effects of cannabis on pain are consistently opposed by studies citing evidence of

minimal-to-no effect.[7] A systematic review of randomized controlled trials determined that oromucosal nabiximols and THC have no effect on pain and opioid consumption in cancer patients with opioid-refractory pain.[7] This evidence was assessed to be very low quality, rendering it impossible to draw meaningful conclusions.[7] Of note, dropout rates due to adverse effects and frequency of nervous system and gastrointestinal side effects were higher with oromucosal nabiximols and THC than with placebo.[7]

Given the volume of low-quality evidence and poor generalizability of results, larger trials are needed to produce results with increased external validity. The current body of knowledge on cannabis use in palliative oncology can be improved with clinical trials to determine accurate drug composition, dose, and means of administration that can be tailored for individual patient indications.[1]

Effects of Cannabis on General Cognition and Memory

Cognitive impairments observed in cannabis users are especially prevalent in the areas of executive function, memory, and attention.[12] The effects of cannabis are often broken down into three main functional domains: cognition, emotion, and reward/motivation.[13] In the literature, cognitive impairments associated with cannabis have been correlated with frequency, quantity, and duration of use.[12] It has been thought that cannabis negatively impacts the domains of cognition, emotion, reward, and also has the potential to blur the lines between functional processes.[13] Manza and colleagues recently tested the hypothesis that the domain of emotion in young adults with cannabis use disorder (CUD) has the potential to interfere with the cognitive domain and inhibit normal cognitive control.[13] This hypothesis takes into account the observation that craving and inhibitory control appears to decrease less in adolescents following intoxication than in adults.[14] By measuring functional magnetic resonance imaging (fMRI) activation to emotional stimuli, it was demonstrated that individuals with CUD had impaired segregation between cognitive and emotional processes.[13] This finding may underlie the observation that cannabis users have poor cognitive control and decision making in emotionally-demanding circumstances.[13] These results are supported by the findings of electroencephalography (EEG) studies, which showed that cannabis users have decreased delta and increased theta, beta, and gamma power in the resting state.[15] These EEG findings suggest that cannabis users experience increased cortical activation during rest that may reflect disinhibition of inhibitory processes that interferes with normal cognition and result in a less efficient, "noisy" brain.[15]

The effects of cannabis on cognition can be subdivided into effects observed with acute use and those observed with chronic use or dependence. It is known that during the acute intoxication period, episodic memory and attention are negatively impacted while impulsivity is increased.[16] A recent randomized, placebo-controlled, double-blind study demonstrated that acute cannabis use impaired working memory and verbal memory.[17] Working memory, verbal, and visual memory have also been shown to be impacted more during acute intoxication in subjects with the Val COMT allele, which is thought to be a link between cannabis and schizophrenia.[16] The effects of cannabis on cognition have also been compared with those of tobacco as the two substances are frequently co-administered during recreational use.[17] It was determined that tobacco alone enhances working memory and may have the potential to offset the effects of cannabis on delayed though not immediate verbal recall.[17] In a specific test of memory impairment, the role of cannabis in relation to false memory production was tested using the Deese/Roediger-McDermott (DRM) paradigm.[18] The performance on the DRM of intoxicated regular cannabis users was compared to that of sober regular cannabis users and cannabis-naïve controls.[18] False memory rates did not vary significantly across groups, but both intoxicated and sober regular cannabis users were more likely to recognize unrelated items, indicating that their memory association with previously learned words was low compared to that of controls.[18] Controls also demonstrated overall greater memory accuracy than both groups of cannabis users.[18] Of note, it has been noted in the literature that frequent cannabis users (four or more days per week) exert significantly poorer effort on tests of learning and memory compared to controls.[19] Thus, effort performance should be controlled for, in studies assessing cognition in frequent cannabis users.[19] Similarly, family and background factors must be controlled for in studies of the effects of cannabis on IQ and executive function, especially in adolescents.[20]

A recent study showed that heavy, chronic abusers of solely cannabis had memory impairment in the Rey-Osterrieth Visual Memory Test.[2] The same study also demonstrated that not only are chronic cannabis abusers inclined to have memory impairment but also are likely to develop significant brain dysfunction that involves the visual-motor system as assessed by the Bender Visual-Motor Gestalt test.[2] When the cognitive domains of chronic cannabis users were evaluated following short-term (mean 15 hours) abstinence and compared to those of chronic tobacco users, cannabis users were found to have poorer overall learning, delayed recall, greater interference, and increased forgetfulness.[21] They also exhibited slower reaction times during information processing and sustained attention tasks.[21]

To further investigate the marked cognitive impairments that have been associated with chronic cannabis use in the literature, Borgan and colleagues conducted a meta-analysis of studies from the EMBASE, MEDLINE, and PsycINFO databases to assess the effects of partial CB1 receptor agonists on spatial and non-spatial memory.[3] THC (1.6–5 mg/kg), a partial CB1 receptor agonist, was shown to significantly impair non-spatial memory in humans while high THC doses (67 mg/kg) additionally impaired spatial memory.[3] THC was also shown to impair visuospatial memory in monkeys and non-human primates.[3] Chronic THC administration did not significantly impair spatial or non-spatial memory in rodents, but evidence of this effect in humans was inconclusive.[3]

The study of the effects of cannabis use on general cognition and memory has led to inquiry into how these effects are moderated by abstinence versus decreased use.[12] The treatments for substance use disorders have historically aimed for abstinence as the end goal.[12] It has become increasingly evident that this approach does not capture patients who significantly reduce their substance use without achieving abstinence.[12] A study of individuals who were currently or formerly in treatment for CUD found that compared to heavy users, individuals who had decreased their use (to less than or equal to three days per week) had similarly improved global health, appetite, and depression outcomes to those who became abstinent.[12] Still, only those individuals who abstained from cannabis use demonstrated improved cognition per the Reported Outcomes Measurement Information System (PROMIS).[12] Despite the observation that only abstinence can improve cognitive function in former cannabis users, Mouro and colleagues tested the hypothesis that the administration of an adenosine A_{2A} ($A_{2A}R$) receptor antagonist could revert the effects of synthetic cannabinoids on recognition memory.[22] The $A_{2A}R$ receptor antagonist istradefylline was shown to revert memory deficits induced by chronic cannabinoid exposure, likely via mitigation of synaptic plasticity impairment that occurs in the CA1 area of the hippocampus following cannabis exposure.[22]

Effects of Cannabis on Neurologic Structures and Neural Activation

Despite cannabis being the most commonly used illicit drug in the world per the United Nations Office on Drugs and Crime, the long-term consequences of its use are not well known.[23] Given that it has been shown that subtle cognitive deficits are evident even seven days following heavy cannabis use, it is thought that cannabis use also has

lasting effects on brain structure and function.[23] Structural neuroimaging studies have continued to show that cannabis users exhibit abnormalities in hippocampal volume and gray matter density. There is also strong evidence in the literature for damage to white matter resulting from cannabis use, as this is where CB1 receptors are highly concentrated.[24] It remains unclear if these observations of abnormal brain structure and activity are a consequence of or a risk factor for cannabis use.[23] There is limited evidence in supporting the use of cannabis over gold standard therapy for restoration of the central nervous system in conditions such as epilepsy, schizophrenia, or multiple sclerosis.[24]

As discussed previously, adverse effects of cannabis on working memory have been described extensively.[25] Working memory is an executive function that develops largely during adolescence.[25] It has been shown that executive function is more impaired in adolescent frequent cannabis users than in adult frequent cannabis users.[14] In a study of 75 adults with longitudinal assessments of cannabis use, early age of onset of cannabis use was associated with reduced posterior parietal cortex (PPC) activation on fMRI.[25] PPC activation was shown to significantly mediate reaction times during the spatial working memory task.[25] In chronic cannabis users, greater cumulative cannabis use was associated with increases is dorsolateral prefrontal cortex (DLPFC) activation.[25] Interestingly, the changes observed in PPC activation did not differ between individuals with single reported use and those with repeated use, suggesting that these effects represent substance use risk factors rather than exposure effects.[25] Further investigation into this area using meta-analysis found that in adult cannabis users, brain activation was increased in the superior and posterior transverse temporal and inferior frontal gyri.[26] Activity in the striate area, insula, and middle temporal gyrus was decreased in adults. In adolescents, activation was increased in the putamen and inferior parietal gyrus.[26] It is thought that these alterations in neural activation during cognitive activation tasks reflect compensatory neuroadaptive changes that occur in users of cannabis.[26] These compensatory changes may reflect less efficient neural strategies being used by cannabis users to achieve the same results as non-users.[27]

The negative neurocognitive effects of cannabis have been explored disproportionately more than the potential positive effects of the drug.[28] One of the reasons people use cannabis recreationally is to increase creativity and, in some circumstances, enhance the experience of the external environment including visual and auditory stimuli.[28] Cannabis has been linked to certain genres of music as well as general appreciation of music throughout history, but there has not been any literature on the potential interaction of cannabis and the experience of listening to music.[28] Freeman and colleagues conducted a study in which cannabis

users were exposed to inhaled cannabis without CBD, cannabis with CBD, and placebo.[28] When the response of these individuals to music was measured using fMRI, it was determined that cannabis without CBD decreased response to music in bilateral auditory cortex, the right hippocampus/parahippocampal gyrus, and the right ventral striatum.[28] The ventral striatum is known to be involved in the processing of reward and positive emotion, suggesting that cannabis may decrease pleasure associated with listening to music.[28] Interestingly, administration of CBD with cannabis improved connectivity between the ventral striatum and auditory cortex.[28] This observation was in line with the hypothesis that CBD balances out certain negative effects of cannabis.[28]

As discussed extensively above, there is a substantial body of literature supporting a relationship between cannabis use and schizophrenia.[29] To further investigate this relationship, fMRIs were obtained from patients with schizophrenia and patients with bipolar disorder.[29] One subset of patients had a history of cannabis use while the other subset contained controls with either schizophrenia or bipolar disorder but without previous cannabis use.[29] When controlling for tobacco use and alcohol use disorders, it was determined that use of cannabis prior to onset of illness was associated with cortical thinning in the caudal middle frontal gyrus.[29] No structural brain changes associated with concomitant cannabis use were identified in patients with schizophrenia or bipolar disorder.[29] Interestingly, individuals with psychosis have been shown to have reduced gray matter density compared to healthy controls. This effect disappeared when the psychosis group was stratified by adolescent cannabis use.[30] This result suggests that adolescent cannabis use can prevent or improve neural impairments in patients with psychosis though this requires more careful evaluation.[30]

Cannabis Use and Head and Neck Cancer

When considering populations of patients with diagnosed head and neck cancer (HNC), a prospective study of 879 HNC patients at a single tertiary center in Canada from 2011 to 2014 compared 74 patients who were cannabis users to 805 non-users.[32] Compared to non-users, cannabis users were less likely to be married and had less significant tobacco smoking histories.[32] Cannabis users differed in proportion of cancers stratified by primary site, with a statistically significant difference in rates of oropharyngeal cancer (63.5% vs 19.9%).[32] Similar rates of cancers of the oral cavity, hypopharynx, and larynx were observed between the two groups.[32] Oropharyngeal cancer in cannabis users was more likely to be p16+ (95.7% vs 82.5%), indicating a predilection for HPV-associated HNCs.[32] Cannabis users were more likely to receive

chemoradiation and less likely to receive surgery alone compared to non-users.[32]

With respect to HNC risk, cannabis is often viewed as relatively harmless, especially when compared to tobacco. It has recently been demonstrated that the consumption of cannabis through smoking produces carcinogens—nitrosamines, polycyclic aromatic hydrocarbons—that are similar to those produced by smoking cigarettes.[33] In addition to these known carcinogens, cannabis smoke contains immunosuppressants and a mixture of potentially mutagenic chemicals.[33] When cannabinoids bind to CB1 and CB2 receptors located specifically on immune cells, downstream processes can exert strong effects on immune cell function and can alter inflammatory processes. Despite these findings, cannabis, unlike tobacco and alcohol, has not been established as a risk factor for head and neck cancer.[33] Still, basic science studies have demonstrated the mutagenicity of cannabis *in vitro*.[33]

Although a causal relationship between cannabis and HNC is not yet supported by literature, there is a significant effort dedicated to expanding research in this field. A case-control study of 173 cases and 176 controls, at Memorial Sloan Kettering conducted in 1999 supported a statistically significant increase in the odds ratio (OR) of 2.6 for the development of HNC in cannabis users, a significant dose-response, and overall increased risk for subjects younger than 55. Several subsequent studies were not been able to replicate these findings.[33] More recent studies have considered the interaction between cannabis and HNC risk on a molecular level. It is well known that epidermal growth factor receptor (EGFR) and its downstream elements are overexpressed in most cases of head and neck squamous cell carcinoma (HNSCC).[34] A study conducted in 2015 of 83 male glottis cancer patients compared three distinct populations: non-smokers, cigarette smokers, and cannabis smokers with immunohistochemical staining for EGFR, protein kinase B, nuclear factor kappa B p50, and cyclooxygenase 2.[34] Significant correlation between overexpression of the EGFR cascade and cannabis smoking was shown.[34] This evidence points to a direct association between cannabis smoking and increased risk of laryngeal cancer via overexpression of the EGFR cascade.[34]

Other clinical studies have considered cannabis with respect to the recently trending microbiome. Cannabis usage has been linked to increased incidence of precancerous mucosal histology in both HNC and bronchi by several studies.[35] A cross-sectional study conducted in 2019 of 20 cannabis users and 19 non-users sought to determine if chronic inhalation-based exposure to cannabis was associated with changes in oral microbiota at the two most common sites of HNSCC: the oropharynx and the lateral border of the tongue.[35] The lateral

tongue site showed microbial changes with cannabis use (decreased *Ca pnocytophaga*, *Fusobacterium*, and *Porphyromonas*), but these were inconsistent with changes seen in cancer.[35] Results from the oropharynx were mixed (higher levels of *Selenomonas* and lower levels of *Streptococcus*), but overall more consistent with the malignant state.[35] As described above, cannabis usage is associated with HPV-induced SCC, correlated with increased frequency of use. It has been proposed that cannabis-induced changes to the oropharyngeal microbiome and to the general immune state may explain both of these observations, but further research is needed.

Unsurprisingly, the literature surrounding cannabis and head and neck cancer begs expansion and clarification. An ideal study would elucidate the existing evidence by testing the effects of cannabis induction of a naïve host on the immune state, oxidative changes, and development of cancer.

Cannabis and Addiction

Various theories on cannabis addiction have been formulated over recent years, most notably, the villainization of cannabis as a "gateway drug" that predisposes an individual to becoming a habitual user of "harder" substances.[36] Research in this area has considered the effects of cannabis both on neural substrates via cannabinoid receptors and on learning mechanisms that are common to all reward-seeking behaviors.[36] At present, it appears that the three-stage neurobiological model of addiction proposed by Koob and Volkow applies to CUD.[37] The framework in this model involves three major neurocircuits: the binge/intoxication stage driven by the basal ganglia, withdrawal/negative affect stage driven by the amygdala, and the preoccupation/anticipation stage driven by the prefrontal cortex.[37] More recently, it has been suggested that the cerebellum seems to be involved in the pathogenesis of drug addiction and interestingly has been shown to contain a high density of CB receptors.[38]

While it is true that most regular cannabis users do not develop addictive use patterns, recent epidemiologic trends suggest that an increasing number of individuals are living with some kind of CUD.[39] In fact, 10% of individuals who ever use cannabis meet criteria for lifetime cannabis dependence.[40] It is thought that 50%–60% of variance in cannabis use disorders is linked to an addictive genetic effect.[40] A meta-analysis that compared individuals meeting DSM-IV criteria for cannabis dependence to cannabis-exposed controls found a cluster of SNPs on chromosome 10 that was associated with a vulnerability to cannabis dependence in individuals of European ancestry.[40] This work, while

preliminary, represents a step toward identifying risk factors that are associated with cannabis dependence and may help identify vulnerable individuals.[40] The importance of understanding the genetic etiology of cannabis dependence and recognizing at-risk individuals is underscored by the recent findings that prevalence of CUD increases with time since initiation of use is higher in individuals age 12–17 compared to those 18–25.[41] This area of research may also pose special interest given evidence that changes in gene expression induced by cannabinoids may persist into subsequent generations via alterations of the epigenome.[42]

Given that current knowledge of cannabis addiction or dependence is limited, therapeutic options for CUD are lacking.[39] As is known from extensive study of alcohol and tobacco dependence, success of intervention in individuals with substance addiction relies on intact emotional and cognitive function.[39] At present, there is concern in the literature that chronic cannabis use can result in lasting cognitive impairments stemming from altered processing in brain regions such as the prefrontal-limbic network.[39] The studies of these effects are limited to short-term abstinence from cannabis use, making it is somewhat unclear which functional impairments recover and which persist over prolonged phases of abstinence.[39] A recent study on the effects of chronic cannabis use, in dependent cannabis users, on emotional processing after extended (> 28 days) periods of abstinence, demonstrated increased response of the medial orbitofrontal cortex (mOFC) and increased mOFC-dorsal striatal and mOFC-amygdala coupling in response to negative emotional stimuli in dependent cannabis users.[39] Processing of positive stimuli was similar in cannabis users and controls. Since the mOFC has been consistently implicated in addiction in the literature, these results suggest that chronic cannabis use may result in addictive changes that cause persistent modifications in emotional processing.[39]

Interestingly, neuroplastic changes in mOFC-striatal connectivity are thought to be implemented in the development of substance addiction.[39] Thus, the switch from decreased mOFC-striatal coupling to increased coupling, that is observed in chronic cannabis users as abstinence continues, may reflect the development of dependence.[39] It is also thought that the switch from ventral to dorsal striatal coupling with the prefrontal cortex may underlie the transition from voluntary to habitual or dependent drug intake, reflecting decreased inhibitory processing.[39]

Conclusion

Societal and legal perceptions of cannabis have been shifting over recent years. As of July 2019, 33 states and the District of Columbia have implemented or voted in favor of medical cannabis programs.

Additionally, eleven states and the District of Columbia have legalized recreational cannabis. Thus, it has become imperative to improve current understanding of both the basic science and clinical applications of cannabis.

This review paper provides a brief overview of medical cannabis and its role in the treatment of chronic pain, as well as its adverse effects on general cognition, memory, neurologic structures and neural activation, head and neck cancer, and addiction.

Currently, most of the evidence regarding cannabis stems from cross-sectional studies of recreational use and thus cannot be used to establish causality. In addition, studies are limited by factors such as small sample sizes, strict exclusion criteria which limit external validity for patients with significant comorbidities or history of substance abuse, and discrepancies between study design parameters, such as frequency of cannabis use. Evidence drawn from systemic reviews are often assessed to be of very low quality, making it impossible to draw meaningful conclusions. Given the volume of low-quality evidence and poor generalization of results, larger trials are needed to produce results with increased external validity. In areas where cannabis is no longer illegal, it may be possible to directly measure the potency of consumed cannabis either by using manufacturing data or by obtaining and assaying cannabis samples. ✤

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