For Submission to AJP

Word Count: 5055
Figures: 0
Tables: 0
Supplementary Material: 0

Pre-Clinical Evidence of the Risks and Consequences of Cannabis Exposure to Youth

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The authors report no competing interests.

ABSTRACT

Objective: This review of the scientific literature examines the pre-clinical data about the adult consequences of exposure to cannabis in youth. We examine four areas of concern potentially affected by cannabis exposure: cognition, emotional functioning, risk for psychosis, and addiction in the animal and human literature.

Method: A literature search was conducted through PubMed, PsychInfo, and Google Scholar with no publication date restrictions. The search terms used were “cannabis”, “marijuana”, “delta-9-tetra-hydrocannabinol”, “THC”, and “cannabinoid” crossed with “adolescent”, “use”, “exposure” “deficit”, “impairment”, “alteration”, “development”, “maturation”, “adult”.

Results: A large body of pre-clinical and clinical data points to a strong correlation between adolescent cannabis exposure and negative emotional and cognitive outcomes in adulthood. While methodological limitations of current human research cannot establish causality, the animal literature clearly indicates that youthful exposure to cannabinoids is linked to long-term consequences affecting multiple domains of function, which can last long after the drug has been discontinued, shares commonalities with those deficits reported in adult populations who began using cannabis in adolescence.

Conclusions: There is compelling evidence, based on data in the current literature, which suggests that cannabis may adversely affect the developing brain. Future research will require carefully designed pre-clinical studies that can assess molecular, structural, and behavioral outcomes, as well as prospective studies in humans, in order to elucidate the full range of potential consequences of adolescent cannabinoid exposure on development and into adulthood.

Introduction

Not since the end of alcohol prohibition in 1933, has the United States been confronted with such widespread support for the legalization of a federally criminalized recreational substance. The spreading legalization of cannabis across the United States has led to the increasing availability of highly potent strains of cannabis rendered in a variety of forms and modes of consumption, along with an expanding list of synthetic cannabinoids. Currently, 23 states have sanctioned the use of medicinal cannabis to varying degrees, while five of those states and the District of Columbia permit legalized recreational use by adults. The course is clear – legalized cannabis is among the fastest growing markets in the U.S., and may continue growing as an additional 18 states are projected to legalize recreational use, and the industry projected to increase by 11 billion dollars, by 2020 (3).

This has led to a growing concern over the potential risks involved in the use of this expanding array of cannabis products (1, 2). While cannabis may be a less harmful recreational drug, in some respects, than tobacco or alcohol when used by adults (1), studies demonstrate that exposure to cannabis during sensitive developmental periods may lead to cognitive and emotional impairments, with the potential to persist far into adulthood, and, in many cases, long after the drug has been discontinued. Even though laws generally deny legal access to cannabis products by people under 21 years of age, the reality is that younger people readily acquire these substances just as they have been able to do with alcohol and tobacco. Among high school seniors alone, the use of cannabis has eclipsed the use of cigarettes in recent years, with 38.6% having used cannabis in the past year and 6-7% reporting daily or almost daily use (4).

Beyond the prevalent consumption of cannabis and its main psychoactive constituent, tetrahydrocannabidiol (THC), synthetic cannabinoids are rapidly increasing in popularity and use. Most of these compounds are new to modern medicine and are sold without penalty to children and adults alike as new forms are routinely synthesized in order to circumvent lagging regulatory and legislative efforts. These compounds can have very different pharmacological actions, and produce different symptoms than cannabis-based products, with sometimes fatal outcomes (2). Yet as the frequency, potency, and variety of cannabinoid use among youth continues to evolve, their use in adolescence – whether medicinally or recreationally – remains untested and of unknown safety.

Current Findings and Applications of Clinical Research

Adolescent cannabis use has been associated with a variety of negative later life outcomes, with alterations found spanning the domains of cognition (5), memory (6), mood, and anxiety (7); increasing the possibility of future suicidality (7), as well as increasing the risk of developing symptoms of bipolar disorder(8), psychosis (9), and later substance dependence (10). Longitudinal cohort studies have found adolescent cannabis users to be more likely to report lower levels of educational attainment, higher rates of unemployment and welfare dependence, lower levels of relationship satisfaction, and an overall diminished experience of life satisfaction (11). These negative consequences have been found to be more prevalent among those who initiated use earlier in life, as well as those who consumed larger doses and at higher frequencies as adolescents (7, 8, 10). Furthermore, a degree of genetic predisposition has been suggested in studies primarily of psychosis. The cannabinoid receptor-type 1 (CB1R) gene, which is involved in modulating the intoxicating effects of cannabis, has certain genetic variants that increase an individual's risk for developing schizophrenia (12, 13). Additional genes key to nervous system development and maintenance, mainly COMT(14, 15), AKT1, BDNF, and NRG1 (16), have variants implicated in increasing the risk for developing psychosis in individuals to use cannabis in adolescence, but not those who first begin cannabis use in adulthood.

Cannabis also seems to have a cross-sensitization effect with a variety of other drugs. Adolescent cannabis users are found to be more likely to abuse and become addicted both to cannabis itself, to nicotine, and to other illicit drugs later in life. This fact is becoming of an increasing public health concern, as the recent evidence has shown that cannabis use in youth can lead up to a four-fold risk for developing nicotine dependence later in life, even among those who did not begin using nicotine until reaching adulthood (17). This relationship between cannabis and nicotine is of particular importance, as the

recent decline in the trajectory of adolescent cigarette use could be at risk for reversal in the wake of increasing cannabis use by young people.

There are limitations to keep in mind when considering the current literature on adolescent cannabis exposure. Inherent to human clinical and epidemiological studies is the difficulty of controlling for an entire landscape of potential confounders, limiting the ability of those studies to establish connections beyond associations. Imaging studies often suffer from a low number of participants, while behavioral measures of human function vary widely in their precision and concordance. As such, we cannot rule out a view of cannabis use and its adverse sequelae as interdependent associations within a common liability model, in which the early use of a drug is seen as one factor among other, possibly equally important factors that predispose an adolescent to escalating illicit drug use. Cannabis use, for example, is closely linked with a collection of adolescent behaviors that themselves are known risk factors for the poor life outcomes associated with early cannabis use; including among them disruptions in education, risky sexual behavior, delinquency, and early exposure to drugs of abuse other than cannabis (11, 18). Some studies have even failed to replicate findings of functional deficits in adults who used cannabis as adolescents when controlling for one or more of these confounders (19, 20). It is very likely that common liabilities that predispose people to the use of cannabis, especially to early and heavier use, also skew the effects of other drugs on the brain (21) and/or contribute to other decisions with negative consequences. In order to obtain further insight into the potential effects of cannabis on the developing brain, a new field of study in animal models has emerged over the years, in which the effect of cannabis can me measured directly on the adolescent brain.

Animal Models of the Behavioral and Molecular Consequences of Adolescent Cannabis Exposure

Given the limitations of existing clinical studies to shed light on potential neuropsychiatric consequences of adolescent cannabis exposure and establish causality, it is important to examine neurobiological effects and causal mechanisms in animal models. Preclinical studies of animal models enable researchers to control for premorbid traits, as well as controlling for the duration, amount and age of cannabis exposure, and even the length of the drug free period after drug cessation. Control over these factors allows assessment of whether cannabis exposure during youth carries long-term consequences in adulthood.

The following studies summarized in this review examine the effects of exposure to both the two most prevalent phytocannabinoids found in cannabis, specifically THC and cannabidiol, as well as a variety synthetic cannabinoids of subtly differing pharmacologies (22, 23). Rodent models of adolescent cannabis exposure use paradigms that initiate cannabinoid treatment anytime between post-natal day (P)21, and P44, which are the rodent equivalents of early onset and later onset in adolescence, respectively; followed by a washout period surpassing the long elimination half-life of cannabinoids. Behavioral and molecular outcomes are then examined starting at P60, the onset of adulthood in rodents (24), or sometime shortly after. This common paradigm is designed to assure that any deficits found in the adult animals are not the result of the acute effects of residual circulating cannabinoids; but rather can be attributed to changes in the brain that are a result of adolescent-onset treatment. As in humans, the adult sequelae of adolescent cannabinoid exposure in animals have been found in altered outcomes of cognition, affect, psychosis, and gateway effects to other drugs of abuse. These effects can vary by the sex and strain of the animals being examined (25); as well as by the age of first exposure, the duration of treatment, the dosage, and the type of cannabinoid used.

Outcomes in Memory and Cognition

Persistent deficits in adult cognition and memory were among the first reported outcomes of adolescent cannabis exposure in rodents. These cognitive deficits were initially demonstrated in a series of experiments lead by Fehr and Stiglick et al., which examined learning and memory in adolescent rats following a period chronic cannabis administration. THC was extracted from whole cannabis leaf and administered to rats at a dose of 20 mg/kg/day for periods varying between 1-6 months, a paradigm comparable to moderate to high use in humans. Cannabis treatment began in rats with average body weights of 120 g, which is consistent with average weights found in adolescent rats (P35-P44), or 270 g, which is consistent with weights in early adulthood (P60) (26). One month or more after drug discontinuation, those animals who received cannabis in adolescents displayed deficits in maze learning tasks (27, 28) and in an avoidance learning task (29), while those first exposed to cannabis as adults did not differ from controls. These results suggest greater learning impairments when high doses of

prolonged cannabis exposure occurs during adolescence, and relatively little cognitive dysfunction when cannabis exposure occurs in mature adult animals (30). The authors noted that the cognitive deficits caused by chronic cannabis exposure were similar to those in rats with hippocampal lesions (29) and suggest that the cognitive dysfunction that is associated with adolescent cannabis exposure is at least in part mediated by the hippocampus. It's important to note, that lower doses of THC, in the range of 10 mg/kg, did not produce significant learning impairments in rats (27) indicating that only prolonged exposure to high does of cannabis extract in adolescence were associated with learning deficits in adulthood.

More recently another behavioral paradigm, object recognition, which measures working memory, and a test measuring motivation were examined in juvenile and adult rats after they were chronically treated with the synthetic cannabinoid agonist WIN 55,212-2 (WIN) either as adolescents or adults (31). Rats were given 20 injections of WIN for 25 days followed by a 10-day drug free hiatus before the onset of behavioral testing. Adult rats that were exposed to WIN in adolescence showed impaired object recognition and a decreased in their break point in a progressive ratio task, indicating reduced working memory and reduce motivation. In contrast, the rats receiving WIN in adulthood showed no behavioral deficits, suggesting increased vulnerability to cognitive and motivational deficits after cannabinoid exposure in adolescent rats. Another investigation examined the influence of adolescent cannabinoid exposure on memory functioning and hippocampal microstructure (32). Adolescent and adult rats were administered THC every other day for twenty days. After a 10-day cessation period, the animals were tested in the novel object recognition task, and protein expression in the hippocampus was examined 7 days later. The THC-exposed adolescent rats had impaired object recognition, but not the adults. Further, compared to adults, THC-exposed adolescent rats had a greater number of differentially expressed hippocampal proteins with overall greater abnormalities in hippocampal protein expression, affecting proteins functioning in oxidative stress, cell signaling, metabolism, and cytoskeletal structure. Together, these results provide molecular and behavioral evidence of adolescent vulnerability to cannabinoid-induced memory impairments. The authors further implicate the hippocampus as a region that may be affected by adolescent THC exposure.

The cognitive sequelae of adolescent cannabis exposure may also vary by sex. Separate studies utilizing similar procedures examined the effects of cannabis in female and male rats (33, 34). The cannabinoid agonist CP 55,940 (CP) was administered to adolescent and adult rats of both sexes in increasing doses for 21 days, and behavioral assessments performed 21 days after drug withdrawal. Female rats treated with the cannabinoid during adolescence, but not those treated in adulthood, exhibited impaired working memory in the object recognition test (33), whereas while working memory deficits were found in both adolescent-onset and adult-onset treated males, there was no effect of age of treatment on the magnitude of these deficits (34).

In general, these pre-clinical studies suggest an increased susceptibility to persistent cognitive deficits in adulthood as a consequence of cannabinoid exposure in adolescence, particularly in the domains of learning and memory. These deficits are distinctly absent in adult animals in which exposure to cannabinoids begins after the adolescent period has passed. Among those who display deficits from adolescent exposure, the outcomes can vary by sex and by the cannabinoid used; and perhaps most importantly, the effects are mainly seen at higher dosing regimens, suggesting that not all cannabis using populations may be equally susceptible to the developmental consequence of cannabis exposure. The being said, these findings also points to the potential risk that the rising potency of cannabinoid products and the synthetic products that are available may result in increase long-term impairment among adolescent-onset users.

Affect and Anxiety

Establishing a connection between early cannabis use and later emotional problems in humans demands that we eliminate major confounders. First and foremost, people with premorbid mental health issues often use cannabis to self-medicate symptoms of anxiety and depression, and these symptoms can re-emerge and become exacerbated following cessation. Meanwhile, withdrawal from prolonged cannabis use is now known to instigate anxiety and depressive symptoms in its own right (35), While we remain unable to eliminate all confounders from human research, paradigms examining emotionality in animals have demonstrated a variety effects of adolescent cannabinoid exposure on affective, anxiety and motivational behavior in adulthood.

Compared to rats first exposed to THC as adults, rats treated with chronic THC as adolescents demonstrate increased anhedonia, or a lack of motivation to seek out an enjoyable stimulus, as measured by decreased voluntary sucrose drinking in the sucrose preference test (36). Adolescent-treated rats also demonstrated increased anxiogenic behavior described by decreased engagement in the social interaction test, compared to their counterparts treated in adulthood (32). Rats pretreated with the synthetic cannabinoid CP as adolescents, but not those pretreated as adults also demonstrated increased anxiogenic behavior in the social interaction test (33, 34). Adolescent pretreated with CP also displayed decreased motivation in adulthood as measured by a decrease break point in the progressive ratio task, which measures motivational strength by requiring progressively more effort to achieve the same food reward (31).

As with the adult cognitive sequelae of adolescent cannabis exposure, there exist sexual dimorphism of both the molecular and behavioral long-term affective consequences of early cannabinoid exposure. Biscaiaet al. (37) provided some of the earliest evidence for sex-divergent affective consequences of adolescent cannabinoid exposure, in this instance, to CP. Compared to males, CP pretreated females displayed increased anxiety behaviors as measured by decreased exploration in the open field and hole board test. Alternatively, the synthetic cannabinoid HU-210 increased the peak corticosterone release and HPA axis response to acute restraint stress in adult male, but not female rats, exposed to the drug in adolescence. Furthermore, HU-201 reduced the density of BrdU-ir cells and overall neurogenesis in the dentate gyrus of those males exposed as adolescence, while females remained unaffected (38).

Depressive behaviors have been found in female rats pretreated with THC in adolescence as modeled by increased despair in the forced swim test (36, 39), though one of these two studies found that both sexes experienced anhedonia equally as adults (36). The sex-specific depressive phenotype was additionally associated with significant molecular alterations found in brains of these female rats, affecting the nucleus accumbens, hippocampus, and prefrontal cortex. Specifically, adult female rats that demonstrated a depressive behavior pattern following THC exposure in adolescence also presented with known neuronal markers of depression; including reduced baseline CB1 receptor density and G-protein coupling in the ventral tegmental area and nucleus accumbens, in addition to decreased CREB activity in the hippocampus and prefrontal cortex, and high CREB activity in the nucleus accumbens coupled with increased dynorphin expression (36).

The affective outcomes of adolescent cannabis exposure are some of the more difficult outcomes to differentiate in animal models. However, the frequent presence of the sexual dimorphism and molecular correlates of these reported behavioral deficits provide a clear case that the adult brain may be at risk for increased symptoms of anxiety and depression as a consequence of adolescent cannabinoid exposure.

PSYCHOSIS OUTCOMES

Schizophrenia manifests with clusters of symptoms that manifest across three functional domains: positive symptoms, i.e. delusions and hallucinations; negative symptoms, which manifest in social withdrawal, poor motivation, and absence of emotional expression or feeling; and lastly, deficits in memory and cognition. Animal models of psychotic disorders are built upon behavioral approximations of these cardinal symptoms. Working memory is assessed to test for cognition, social interaction behaviors model negative symptoms, and drug-induced hyperactivity and prepulse inhibition (PPI), which measures the ability to attain and correctly process information, are measured as approximates of positive symptoms (40). Animal models of the cognitive and negative symptoms of psychotic disorders share close overlap with the animal models of cannabis-induce cognitive and emotional alterations that are previously discussed in this review.

Prepulse inhibition (PPI) is a behavioral measure of sensorimotor gating, or the pre-attentive filtering process of stimuli, which is found to be deficient in psychotic patients and cannabis users at a clinically high-risk for developing schizophrenia; and is the most commonly used model of positive symptoms in animals. In humans, a decrease in PPI is strongly correlated with the presence of schizophrenia and other psychotic disorders, and is also found to be impaired in individuals who use cannabis who are also at high risk for schizophrenia (41). Adolescent exposure to synthetic cannabinoids has been documented to elicit disruptions in PPI in female and male animals (31, 42-44), though PPI disruption as a result of cannabinoid exposure in males has not always been a replicable finding (45). Further indication that these behaviors are useful to model risk for psychosis is established by the fact that the deficit in PPI that are linked to adolescent cannabis exposure can be attenuated following acute administration of the antipsychotic haloperidol, and alternately potentiated by acute

administration of the D2 agonist apomorphine (43). Gleasonet al. (44) implicated a number of biological markers with deficits in PPI and fear conditioning in adult mice following exposure to the synthetic cannabinoid WIN in adolescence. The authors found PPI deficits parallel a reduction in hippocampal metabotropic glutamate receptors type 5 (mGluR5), a receptor that is closely involved in cannabinoid signaling. They consequently also found a sustained change in endocannabinoid turnover within the hippocampus of these mice, suggesting that hippocampal alterations associated with exposure to WIN may contribute to this behavioral deficit. Results are sparser for studies examining THC exposure, however the few that exist suggest that there is no effect of exposure to THC in adolescence on PPI in adulthood (46, 47).

Adolescent THC and WIN exposure also seem to impact adult GABAergic activity, which has shown to be dysregulated in schizophrenia (48). Exposure to WIN only during early- (P35-40) and mid- (P40-45) adolescence was found to elicit enduring down regulation of GABAergic transmission in the PFC, translating to enduring state of PFC network disinhibition in adulthood (49). In addition, adolescent THC exposure has been found to lead to reduced GAD67, the enzyme primarily responsible for GABA synthesis in adulthood, and basal GABA levels within the adult PFC, which correlated to deficits in working memory, social withdrawal, altered emotional reactivity and increased sensitization to the locomotor activating effects of acute PCP (39). Together these findings suggest that early cannabinoid exposure may reduce GABAergic activity in the PFC, which may have consequences related not only for psychotic symptoms, but also to a number of other affective and cognitive impairments. Of particular translational importance is the data regarding COMT, a gene associated with the risk for developing psychosis following adolescent cannabis exposure in humans. By using COMT knockout mice, the authors demonstrated that the COMT-deficient mice expressed a greater disruption in PPI compared to wild-type mice following adolescent exposure the cannabinoids WIN (50) and CP (51).

The relationship between human and rodent genetic and environmental vulnerabilities to early cannabis exposure has been examined in much greater detail than other domains of function. These findings suggest that cannabis, may, under certain circumstances, increase the risk of developing psychosis, and this information may lay down a promising foundation with which to study the often cited, yet not fully characterized, relationship between cannabis use in adolescence and the development of psychotic symptoms.

Cross-Sensitization With Other Drugs

When examining human trajectories of drug use, cannabis exposure almost unanimously precedes the use of other illicit drugs. However, it is not clear, if beyond reasons of accessibility and social norms, which is the most likely reason the use of cannabis precedes other drugs, whether cannabis has an actual effect on the brain that changes the response to other drugs. Animal models are particularly useful to study the effect of cannabis on how the brain later reacts to other drugs because they allow for the careful administration of two drugs in succession while controlling for all other variables. Indeed experiments in animals demonstrate that early cannabis exposure may in fact change the way the adult brain responds to other drugs of abuse.

Like most drugs of abuse, cannabinoids interact to increase dopaminergic activity, suggesting the possibility of reinforcing behavior and cross-sensitization. The endogenous cannabinoid anandamide has been shown to be an effective reinforcer of drug-seeking behaviors, as squirrel monkeys will self-administer anandamide, and it's synthetic analogue R (+)-methanandamide; behavior which can be reversed by pre-treatment with CB1 antagonist rimonabant (52). The manner in which adolescent THC exposure affects addictive behavior, specifically the self-administration of THC in adulthood, cannot be presently examined, as rodents have not been found to self-administer THC under normal conditions. Rodents do, however, self-administer other cannabinoids, and indeed it has been shown that adolescent THC exposure increases WIN self-administration in adult rats. Neurophysiological data from this same study found that early THC exposure lead to reduced ability of WIN to activate dopaminergic neurons in the VTA and to increased levels of dopamine in the NAc. Adolescent exposure to WIN itself also has the capacity to induce cross-tolerance in adulthood, as found in a study demonstrating that adult rats exposed to WIN in adolescence exhibited decreased activation of VTA dopaminergic neurons following individual doses of amphetamine, cocaine, and morphine (53).

THC and WIN activate mesolimbic dopaminergic transmission via mu1 opioid receptor activity in rodents, and cannabinoid-mediated dopaminergic transmission can be subsequently blocked by the general opioid antagonist naloxone

(54). THC self-administration behavior in squirrel monkeys can be blocked by pretreatment with the opioid antagonist naltrexone (55). In addition to the opiate system function in modulating cannabinoid intake and vice versa, the opioid system and cannabinoid system function together to mediate behaviors such as nociception and appetite. Exposure to cannabinoids during developmentally critical periods such as post-natal and adolescence has been repeatedly shown to alter the maturation of the endogenous opioid system (58). Rats exposed to THC in adolescence exhibited greater vulnerability to opiates as adults, as measured by a greater conditioned place preference for heroin (59) and more frequent heroin self-administration (60, 61), coupled with an increase in break-point for heroin reward in progressive ratio task (61). In addition, rats who were exposed to THC in adolescence, then exposed to heroin as adults with a subsequent washout period, demonstrated increased self-administration of heroin in response to stress. This suggests that not only does adolescent cannabinoid pretreatment have the potential to alter adult response to opiates, but that the response is synergistic with stress.

Molecular evidence is emerging to better test the potential cross-sensitization between cannabinoids and opiates. In addition to demonstrating the behavioral effects of early cannabis use on later heroin-seeking, Tomasiewiczet al. (60) showed that this behavior was tightly correlated with upregulation of the opioid polypeptide gene Proenkephaline (Penk), which was also associated with a reduction in histone H3 K9 di- and tri-methylation in the nucleus accumbens shell surrounding the Penk gene. Most intriguingly, the authors were also able to alter drug administration bi-directionally: by inducing Penk overexpression in THC-naïve rats, they increased heroin self-administration to levels seen in those exposed to THC in adolescence; and conversely reduced heroin intake by reducing Penk expression in animals exposed to THC in adolescence. In addition to the effect on the Penk gene some of the rewarding properties of cannabis as well as its long-term effects on the opioid system are likely mediated, as with other drugs, by dopamine.

There is clear evidence here that early cannabinoid exposure can adversely affect future drug seeking behaviors in animals. Moreover, a growing number of studies are demonstrating a unique link between cannabinoids and opioids and the potential priming effects one has on the addictive properties of the other. While this does not address the issue of whether early cannabis exposure encourages future drug use, it does suggest that adolescent cannabis users may be putting themselves at risk for future problems with drug abuse and dependence, and for the potential additional risk for the development of nicotine or opiate addiction, including opiates prescribed for pain management, in people that were exposed to cannabis in adolescence.

Applications and Limitations of Pre-Clinical Research

A major pitfall of many studies has been the reliance on synthetic cannabinoids, mainly CP55,940 and WIN55,212-2, as the pharmacological challenge in models of adolescent cannabinoid exposure. CP55,940 and WIN55,212-2 are both full agonists at the CB1 and CB2 receptors. None of the known phytocannabinoids in cannabis act as full receptor agonists, while the main psychoactive constituent, THC, is only a partial agonist with significantly decreased binding affinity (62). Synthetic cannabinoids affect rodent behavior with greater potencies relative to THC (63), and rats can be trained to discriminate between these compounds (22, 23), suggesting that each cannabinoid produces a different subjective response. An additional limitation of these treatment paradigms is the widespread use of intraperinteally or intravenous routes of drug administration, which remain epidemiologically irrelevant models for cannabis administration in humans. This distinction is important as injection of cannabinoids has been shown to have psychoactive and physiological consequences that differ from inhalation in both humans and rats (64-66). It is reasonable to expect then, that different mechanisms of cannabinoid administration may lead to differing consequences on adolescent development into adulthood.

The primary method of cannabis consumption in humans is by inhalation of cannabis smoke, which can contain over 60 phytocannabinoids in strain-specific concentrations. Many of these compounds are psychotropic, and all have unique pharmacological profiles (67-69). Most notable is the complex interaction between THC and cannabidiol (CBD), compounds which interact both synergistically and antagonistically in vivo. Exposure to different THC:CBD ratios will elicit very different, ratio-dependent, psychoactive and physiological effects in humans and animals (70), and these effects are reflected in cannabis cultivars of varying THC:CBD ratios as well (71, 72). Inhalation of cannabis smoke specifically has been demonstrated to affect mice differently than standard THC injection (73). And yet inhalation of whole cannabis smoke is rarely

utilized in animal research, especially regarding its effects on maturation. Due consideration must be given, however, to animal studies using high doses of THC or utilizing synthetic cannabinoids, as they are becoming increasingly relevant given the current trends of increasing human consumption of THC concentrates and synthetic cannabinoids such as “K2” and “Spice” (74).

SUMMARY

Pre-clinical research, largely on rodent models, suggests that predisposing genetic or sociocultural aspects do not fully account for the cognitive and emotional deficits observed in adults exposed to cannabis in adolescence. This evidence strongly suggests that cannabis exposure during adolescence may affect brain development and have the potential to result in long-term adverse effects on cognitive and emotional functions. It is important to keep in mind, however, that the animal studies of cannabis exposure, to date, vary greatly in design; and additional research must be conducted with the field aimed at reaching a consensus for the design of an animal model of cannabis exposure in youth, in order to form the most coherent and conclusive understanding possible of how cannabinoids affect the developing brain, and what mechanisms may be targeted for prevention, intervention, and reversal of harm. Regardless of whether cannabis use is the result or the cause of neuropsychiatric sequellae, a history of early cannabis use in youth should serve as a red flag to clinicians for potential impairments in cognitive functioning, and a risk factor for anxiety, depression, suicide and psychosis.

The increasing acceptance of medical and recreational cannabis use in society, and the policy and legislative changes that have followed and occasioned this, are largely based on research and our experience derived from and pertinent to adults. Absent from any risk vs. benefit analysis is a definitive understanding of how cannabis exposure affects young people and their trajectory of neurobehavioral development, or how increased legalization will affect its use, particularly by adolescents, going forward. Consequently, from what we can glean from the existing literature, it is essential that research be pursued that will enable us to fully understand the effects of cannabis consumption, both medicinal and recreational, on youth.

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