Testimony to Senate Committee on Public Health and Welfare
Senate Bill 113
March 15, 2019

Dear Chairman Suellentrop and Members of the Senate Public Health and Welfare Committee:

My name is Michelle Voth. I am the Vice-Chair of the Kansas Association of Addiction Professionals (KAAP) and am here to speak in opposition to SB 133. KAAP is the state's largest addiction services trade association and traces its roots going back to the 1970's. Today, KAAP's membership includes agencies located all over the state providing an array of services from outpatient to residential treatment and prevention services. Our goal is to serve members with advocacy and support to achieve excellence in addiction treatment and prevention. KAAP helps our members provide the highest quality and most up-to-date, science-based services to our clients, our families and our communities. It is in this spirit that we oppose SB 113 that would legalize medical marijuana in our state.

Legalization of marijuana isn't good policy when you consider the following:

- Youth Treatment - Marijuana is the #1 reason children and adolescents are admitted for substance-dependence treatment in Kansas and throughout the country. The availability of substance use disorder treatment for youth is already an identified need in Kansas and could become a greater need in Kansas if SB113 is passed.

- Unintended and real consequences for youth - We know from research that the three primary contributors to substance abuse and addiction are: accessibility of the substance, social acceptance of the substance's use, and perceived risk of harmfulness. Legalizing marijuana (not the components that have been researched) for medical purposes will result in the following:

  Because of increased access and social acceptability, the ability of Kansas youth to understand the harmfulness of marijuana will be reduced. Since 2009, there has been a 52% increase in the number of Kansas students who say there is no risk to using marijuana regularly.

  Please consider that Colorado, which has had legalization for many years now ranks 3rd in the nation for current marijuana use among youth. That is 56% higher than the national average. In 2006, before legalization, Colorado ranked 14th.

  When you look at the data of all the states who have legalized marijuana in any form, the correlation is clear. Legalizing equals greater past month usage by 12-17 year olds. Increase in youth suspensions, expulsions and referral to law enforcement have been also documented in Colorado.

- Lack of Science- Based Evidence – Professionals in the field of addition and prevention are required by their regulatory boards and funders to deliver services and practices that are evidence-based. This bill creates medicine by legislative action that is not supported by research, but rather by anecdotal stories. This bill would legalize the use of all types

of preparations of the cannabis plant, smoked, concentrate and edibles. Unlike medicines that are vetted through the FDA, consumers will not have the protection of knowing in advance the potential harms, contraindications, dosage, etc.

Research has repeatedly demonstrated that reducing alcohol and drug abuse rates in our adults begins in adolescence. Numerous Journal articles also refute many of the claims made by proponents about the supposed benefits of marijuana. A few highlighted studies should be considered:

- American Journal of Psychiatry, January 2018 showed that people who used cannabis in 2001 were almost three times as likely to use opiates three years later, even after adjusting for other potential risks.
- An exhaustive review completed by the National Academy of Medicine in 2017 found that "cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk. Additionally, they found "regular cannabis use is likely to increase the risk for developing social anxiety disorder."

What does KAAP support? We support research. In 2017, the National Institutes of Health supported 330 projects totaling almost $140 million in cannabinoid research. We support education related to the three new medications that have been approved by the FDA one of which treat epilepsy and two others for treating chemotherapy related nausea and to increase appetite in patients with AIDS. We support treatment modalities that are evidence-based and not based on a wish and a prayer that there will be no harm by using a substance that is smoked, not regulated, and that does not afford youth and adults consumer protection.

Yes, many states have enacted similar legislation and are now trying to mitigate the harms that weren't discussed and/or anticipated prior to enactment. An example of groups taking a stand for evidence-base practices, is the Cleveland Clinic. In January 2019, Medscape, a physician journal, reported that this nationally recognized clinic will not be recommending the use of marijuana for its patients. They believe the risks on a patient's health are well documented and the research on the health benefits are inconclusive at best.

Yes, Kansas is one of four states that has not passed medical marijuana legislation. The proponents of this legislation will argue that we are behind the curve. KAAP and those who support the use evidence-based practices would argue that Kansas is ahead of the game. KAAP hopes that Kansas will continue to realize the importance of protecting health, protecting youth, providing for the availability of medicine based on research and realize that the cost of getting this wrong will negatively impact this state for generations to come.

Review

Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review

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With a political debate about the potential risks and benefits of cannabis use as a backdrop, the wave of legalization and liberalization initiatives continues to spread. Four states (Colorado, Washington, Oregon, and Alaska) and the District of Columbia have passed laws that legalized cannabis for recreational use by adults, and 23 others plus the District of Columbia now regulate cannabis use for medical purposes. These policy changes could trigger a broad range of unintended consequences, with profound and lasting implications for the health and social systems in our country. Cannabis use is emerging as one among many interacting factors that can affect brain development and mental function. To inform the political discourse with scientific evidence, the literature was reviewed to identify what is known and not known about the effects of cannabis use on human behavior, including cognition, motivation, and psychosis.

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It is well established that cannabis use causes acute impairment in the ability of the brain to hold information (ie, cognitive capacity). Hence, temporary deficits occur in learning and memory, attention, and working memory.

Does Cannabis Use Affect Cognitive Capacity?

Cannabis use causes acute impairment of learning and memory, attention, and working memory,[1-3] but it is less clear if cannabis use is associated with enduring neuropsychological impairment. Case-control studies comparing nonintoxicated heavy cannabis users with nonusers have fairly consistently shown that heavy cannabis users perform worse on neuropsychological tests. For example, the results from 2 separate meta-analyses[4,5] showed that compared with nonusers, nonintoxicated cannabis users perform worse on measures of global neuropsychological function, with effect sizes for specific neuropsychological domains (executive functions, attention, learning and memory, motor skills, and verbal abilities) of approximately one-third of a standard deviation or less. When analyses in the second meta-analysis[5] were limited to 13 studies of cannabis users with at least 1 month of abstinence, there was no discernible difference between cannabis users and nonusers on neuropsychological test performance, suggesting that neuropsychological functions might recover with prolonged abstinence. Evidence suggests that the magnitude of neuropsychological impairment and the extent to which it persists after abstinence may depend on the frequency and duration of cannabis use, length of abstinence, and age at onset of use.[6]

Emerging evidence suggests that adolescents may be particularly vulnerable to the adverse effects of cannabis use. Adolescence represents a critical neurodevelopmental period characterized by marked synaptic pruning and increased myelination.[7] Moreover, the endocannabinoid system appears to be involved in the regulation of key neurodevelopmental processes,[7] suggesting that the introduction of exogenous cannabinoids during adolescence could disrupt normal brain development. Animal research supports the possibility that adolescence represents a period of heightened vulnerability to cannabis exposure.[7] For example, pubertal rats treated with a cannabinoid agonist showed persistent deficits on object recognition tasks, whereas adult rats did not.[8,9] Accumulating evidence in humans parallels the animal findings.[6] For example, several studies have shown that earlier age at onset of cannabis use is associated with greater neuropsychological impairment,[10,11] and a 2012 population-representative longitudinal study[12] documented that adolescent-onset (but not adult-onset) persistent cannabis users showed neuropsychological decline from ages 13 to 38 years.

Neuroimaging investigations of adolescent and adult cannabis users have yielded somewhat inconsistent findings. Recent reviews have demonstrated that there is fairly clear evidence of structural alterations in medial temporal (amygdala and hippocampus), frontal, and cerebellar regions associated with cannabis exposure.[13,14] However, another recent study[15] that carefully matched participants on alcohol intake reported no evidence of morphological brain alteration among adolescent or adult cannabis abusers, suggesting the possibility that comorbid alcohol use could explain some of the morphological alterations observed in prior research. There is also some evidence that cannabis users have impaired neural connectivity. For example, a study[16] of adults with long histories of heavy cannabis use showed evidence of decreased connectivity in the right fimbria of the hippocampus (fornix) and the splenium of the corpus callosum and the commissural fibers. Finally, functional magnetic resonance imaging investigations have suggested that cannabis users show altered neural activity both in the resting state and during cognitive testing.[14] For example, male adolescent cannabis

users showed increased blood oxygen level–dependent functional magnetic resonance imaging activity in the prefrontal cortex during a novel working memory task, which was interpreted to reflect inefficient processing.[17] This observation is consistent with studies measuring resting functional connectivity in adolescent cannabis users that have documented altered patterns of connectivity affecting interhemispheric traffic[18] and the frontotemporal network.[19,20] Some evidence suggests that cannabidiol, another cannabinoid found in the cannabis plant (although usually at very low concentrations), may protect against some of the harmful effects of tetrahydrocannabinol (THC) on cognition.[21,22]

There are areas that require further research. First, observed differences in neuropsychological test performance, as well as in brain structure and function, might reflect individual differences that precede cannabis use. Progress has been limited by reliance on cross-sectional investigations comparing cannabis users and nonusers. Two longitudinal studies[12,23] with before-and-after neuropsychological testing have shown evidence of within-individual decline in neuropsychological function associated with cannabis use. The findings could not be explained by alcohol and other drug use, psychiatric disorders, low socioeconomic status, or a host of other potential confounds. However, the number of cannabis users in these cohorts was small, and brain imaging was not performed. Yet, neuroimaging findings raise the possibility that smaller regional brain volumes among cannabis users could be partially accounted for by preexisting differences. For example, one prospective longitudinal study[24] showed that smaller orbitofrontal cortex volumes increased risk for adolescent cannabis use initiation, while a study[25] of twins and siblings found that reduced amygdala volumes among cannabis users could be explained by familial factors. Taken together, these findings highlight the need for longitudinal studies that follow up adolescents from before to after initiation of cannabis use and combine neuropsychological testing with neuroimaging. The Adolescent Brain Cognitive Development Study,[26] a large prospective National Institutes of Health–funded investigation of children ages 9 to 10 years who will be followed up for at least 10 years, is being launched to in part meet this need.

A second area that is ripe for further research pertains to the need to reconcile neuroimaging findings with neuropsychological test performance. Current neuroimaging evidence is inconsistent, and alterations in brain structure and function tend not to correlate with decrements in neuropsychological test performance.[27] Larger samples are needed for imaging along with careful consideration of participant characteristics, including comorbid use of alcohol and other drugs and length of abstinence from cannabis.

Third, more work is needed to answer the question "How much cannabis use is too much?" Because many study samples include a large portion of individuals with cannabis dependence (as defined by the *DSM-IV*), it is unclear if the effects generalize to individuals with less severe cannabis use disorders and to more casual recreational users.

Fourth, because of the potential effect of exogenous cannabinoids on brain development, more work is needed to answer the question "At what age is cannabis use most harmful?" In addition to studying the effects of cannabis use on adolescents, research is also needed to understand older adults' susceptibility to cannabis-related neuropsychological impairment. This population experiences changes in brain plasticity and age-related cognitive decline that may make them more vulnerable to the effects of cannabis use.

Fifth, recent evidence suggests sex differences in neuropsychological deficits associated with cannabis use.[1,28] Hence, future work should help clarify mechanisms underlying these potential sex differences.

Sixth, genetic factors such as polymorphisms in the *COMT* (OMIM 116790) and *AKT1* (OMIM 164730) genes may also increase susceptibility to cannabis-related neuropsychological impairment.[29] Other examples include a recent study[30] that showed that THC caused acute impairment of working memory for *COMT* Val/Val carriers (but not Met carriers), as well as another study[31] of 3 population-based cohorts that showed that cannabis use was associated with decreased cortical thickness among male individuals at high (but not low) genetic risk for schizophrenia as indexed by a polygenic risk score. The possibility that individual differences among cannabis users may have significant effects and be predictive of the extent of adverse consequences suggests that recent approaches to leveraging genetic information to create polygenic risk scores might be useful toward advancing the study of cannabis use and neuropsychological function.

Does Cannabis Use Decrease Motivation?

As early as the late 19th century, the Indian Hemp Drugs Commission[32] reported that heavy cannabis use was associated with apathy, defined as reduced motivation for goal-directed behavior.[33] However, it was only after the marked increase in cannabis use of the 1960s that the amotivational effects of chronic cannabis use were linked to impairments in learning and sustained attention. The term *cannabis amotivational syndrome* was proposed by McGlothlin and West,[34] who characterized it as apathy and diminished ability to concentrate, follow routines, or successfully master new material. While there has always been some controversy around the need for defining such a distinct phenotype, there is evidence that long-term heavy cannabis use is associated with educational underachievement and impaired motivation, which have been proposed to be potential mediators of poorer functional outcomes.[35]

There is both preclinical and clinical evidence supporting the view that cannabis use is associated with an amotivational state. In rhesus monkeys, heavy chronic cannabis use or administration has been found to dampen motivation, as measured on progressive ratio and conditioned position responding operant tests.[36] There is preliminary laboratory evidence supporting an association between reduced motivation for reward-related behavior in cannabis users compared with control individuals.[37] Because these findings appear to be related to repeated doses of THC, it is likely that reduced motivation is one pathway to impaired learning, as THC can disrupt reward-based learning.[38] In support of this theory, cannabis users exhibit reduced striatal dopamine synthesis capacity,[39] with an inverse relationship to amotivation. Inasmuch as dopamine signaling sustains motivation,[40] impaired dopamine synthesis could underlie the amotivational state in cannabis users. Similarly, imaging investigations documented decreased reactivity to dopamine stimulation in cannabis users that was associated with negative emotionality and that would also contribute to reduce engagement in non–drug-related activities.[41]

Amotivation in chronic heavy users may also reflect the fact that cannabis itself has become a major motivator, so other activities (eg,

schoolwork) become demoted in the individual's reward hierarchy. Indeed, addiction to the drug occurs in about 9% of users[42] who appear more vulnerable than other users because of a multiplicity of variables, including age at onset, level of use, and environmental and genetic factors.

What remains to be seen is whether changes in the concentration of the active ingredients of cannabis could affect the risk of amotivation or addiction. The cannabis plant contains approximately 100 unique cannabinoid ingredients, with the most researched being THC and cannabidiol. Over the last 30 years, levels of THC in street cannabis have increased.[43] Of these 2 compounds, only THC determines the level of the subjective high. Alongside a blunted dopamine system,[41] chronic heavy use of cannabis is associated with changes in the endocannabinoid system, including reduced levels of anandamide (an endogenous ligand for the cannabinoid receptors) in human cerebrospinal fluid[44] and reduced levels of cannabinoid 1 receptors.[45] Indeed, a growing preclinical literature implicates cannabinoid 1 receptors and their endogenous ligands in the motivational effects of cannabis use.[46] Similar to the association of cannabis use with cognitive impairment, it is impossible to unambiguously establish whether cannabis use is a cause, consequence, or correlate of altered motivation. Further work is needed to distinguish whether the potential amotivational effects are related to cannabis use disorders rather than cannabis use per se.

Does Cannabis Use Increase the Risk for Psychosis?

One of the most persistent controversies vis-à-vis cannabis use pertains to its effect on the risk of psychiatric disorders, particularly psychotic disorders and full-blown schizophrenia. Longitudinal investigations show a consistent association between adolescent cannabis use and psychosis. Cannabis use is considered a preventable risk factor for psychosis.[47] The link between cannabis use and schizophrenia could stem from direct causality, gene-environment interactions, shared etiology, or self-medication for premorbid symptoms, although some researchers have suggested that only the first 3 hypotheses remain open questions.[48-50] The sporadic emergence of conflicting data should not be surprising given the nature of this particular biological problem. For example, the effects of cannabis exposure may be modest in the total population and contingent on the presence of multiple genetic and environmental variables. On the other hand, there remains a lingering and legitimate controversy over what proportion of psychosis risk can be attributed to cannabis use and the extent to which individuals without genetic predisposition can be precipitated into the illness.

Despite this ambiguity, there is strong physiological and epidemiological evidence supporting a mechanistic link between cannabis use and schizophrenia. Tetrahydrocannabinol (particularly at high doses) can cause acute, transient, dose-dependent psychosis (schizophrenia-like positive and negative symptoms).[51] In addition, prospective, longitudinal, epidemiological studies consistently report an association between cannabis use and schizophrenia in which cannabis use precedes psychosis[52] independent of alcohol consumption[53] and even after removing[52,54] or controlling for[55,56] those individuals who had used other drugs. Although the prodromal period before full-blown illness complicates determining whether or not cannabis use precedes symptoms or reflects an attempt to treat them, cannabis use preceded psychosis in these studies.[52,54,57] Moreover, persistent cannabis use after a first episode is associated with poorer prognosis[58] even after controlling for other substance use.[59]

Although cannabis use may have long been discontinued before the onset of psychosis, the age at which cannabis use begins appears to correlate with the age at onset of psychosis, suggesting a causal relationship to initiating psychosis that is independent of actual use.[49,60,61] The association between cannabis use and chronic psychosis (including a schizophrenia diagnosis) is stronger in those individuals who have had heavy or frequent cannabis use during adolescence,[53,54,60,62,63] earlier use,[52] or use of cannabis with high THC potency.[60,62] From these studies, ever use of cannabis is estimated to increase the risk of schizophrenia by approximately 2-fold, accounting for 8% to 14% of cases,[55] with frequent use or use of cannabis with high THC potency increasing the risk of schizophrenia 6-fold.[53] Consistent with this notion, the greater cannabinoid receptor type 1 availability that has been reported in some patients with schizophrenia,[64,65] and which correlates with negative symptoms,[66] may also contribute to an enhanced sensitivity to the psychotogenic effects of cannabis use. It is important to highlight in this context that most individuals who use cannabis do not develop schizophrenia. Therefore, while cannabis use is neither necessary nor sufficient for the development of schizophrenia, available evidence suggests that cannabis use may initiate the emergence of a lasting psychotic illness in some persons (most likely those individuals with a genetic vulnerability),[67] and this finding warrants serious consideration from the point of view of public health policy.

It is becoming increasingly clear that acute psychosis, schizophreniform disorder, and schizophrenia are the result of interactions among many different factors operating at various levels. For example, having a close family member with schizophrenia is the strongest known risk factor for schizophrenia, yet few investigations linking cannabis use and schizophrenia have controlled specifically for familial schizophrenia risk. The results of one study[68] suggested that cannabis use may lead to schizophrenia in individuals with a family history of the disease compared with those individuals without a family history. However, controlling for familial risk in one large epidemiological study[69] considerably attenuated but did not completely eliminate the association of cannabis use with schizophrenia, with odds ratios of 3.3 and 1.6 with 3-year and 7-year temporal delays, respectively.

Possible 3-way interactions among genotype, cannabis use, and psychosis have also been explored. The *DRD2* genotype (OMIM 126450) influenced the likelihood of a psychotic disorder in individuals who used cannabis.[70] Among occasional cannabis users and daily cannabis users, carriers of the *DRD2*, rs1076560, *T* allele had 3-fold and 5-fold higher likelihoods of a psychotic disorder, respectively.[70] The functional *COMT* Val-158 polymorphism has also been reported to moderate the effect of adolescent cannabis use on adult psychosis, such that carriers of this allele were more likely to develop schizophreniform disorder if they used cannabis than noncarriers of the allele.[67] In an experimental THC study,[71] *COMT* Val carriers had greater cognitive impairment after THC exposure and more psychotic symptoms than *COMT* Met/Met carriers. An *AKT1* genotype by cannabis use interaction has also been reported, with those individuals having C/C rs2494732 genotypes and also using cannabis having a 2-fold higher chance of experiencing a psychotic

disorder.[72] In another study,[73] those participants who were carriers of the *AKT1* C/C genotype with ever use of cannabis and daily use showed 2-fold and 7-fold increased likelihoods of a psychotic disorder, respectively, compared with users and daily users who were T/T carriers.

The results supporting the hypothesis that some gene variants influence the likelihood of developing schizophrenia contingent on certain environmental exposure (eg, cannabis use) reflect tentative findings among small numbers of individuals that require replication.[74] An alternative explanation is that individuals at genetic high risk for schizophrenia may be more likely to use cannabis through a shared genetic risk for schizophrenia and cannabis use disorder. Indeed, the recent report from a large genome-wide association study[75] of an association between schizophrenia risk alleles and cannabis use suggests that part of the association between schizophrenia and cannabis use may be because of a shared genetic etiology. However, the use of cannabis with high THC potency was strongly associated with later development of schizophrenia in one study,[63] while the recently reported polygenic risk score for schizophrenia[76] was unrelated to cannabis use or the potency of cannabis used.[77]

Finally, as in chronic or heavy cannabis users,[78] patients with schizophrenia also show reduced volumes in the amygdala and hippocampus.[79] This observation could help explain the worse clinical outcomes in individuals with schizophrenia who use cannabis because those morphological changes are likely to underlie or contribute to the cannabis-associated exacerbation of symptoms seen in schizophrenia.[80]

Conclusions

Decades of ill-informed and porous legal and illegal drug regulations have exacted a devastating public health toll from our society. It is clear that the cumulative effect of nicotine exposure and alcohol use on morbidity and mortality has been staggering, as has the disproportionate criminal justice influence of the "war on drugs" on minority and disadvantaged populations. Current efforts to normalize cannabis use are being driven largely by a combination of grassroots activism, pharmacological ingenuity, and private profiteering, with a worrisome disregard for scientific evidence, gaps in our knowledge, or the possibility of unintended consequences. Given the critical and wide-ranging role of the endocannabinoid system in the brain,[81-83] the increasing prevalence of cannabis use and use disorders over the last decade and the increased THC concentration in cannabis plants, there is a need to clarify which aspects of cannabis exposure (eg, age at initiation, quantity used, frequency of use, duration of use, and potency of cannabis used) confer the greatest risk for the development of cannabis use disorder or for other adverse consequences (ie, cognitive deficits, lack of motivation, or psychosis). In addition, there are many unanswered questions more directly linked to the soundness of hastily implemented policies. For example, will advertising be permitted? What patterns of use and associated toxic effects will emerge if and when "e-joints" become widespread or even the norm among adolescents? How will expanding the pool of pregnant cannabis users affect the developmental trajectories of exposed fetuses? Finally, what are the consequences of secondhand cannabis smoke?

If we stay the current course, we are likely to uncover effects that were rare in the past only because the use was not as widespread as that of legal drugs. Vulnerable populations such as children, adolescents, the elderly, or individuals with other disorders may experience novel toxic effects (as well as the potential benefits). The changing landscape of cannabis use (eg, strains with higher THC potency, new routes of administration ["vaping" and edibles], and novel drug combinations) and a culture of rapidly changing norms and perceptions raise the possibility that our current, limited knowledge may only apply to the ways in which the drug was used in the past.

The areas explored in this article, which reflect only a subset of the multiple effects of cannabis use on the brain and body, belie the ubiquity of the cannabinoid signaling system. Therefore, in addition to expanding our basic research efforts, we should try to learn as much and as rapidly as we can from the ongoing changes in local policies to minimize the harms and maximize the potential benefits.

ARTICLE INFORMATION

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