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Nicotine and Cannabis Use in Attention Deficit Hyperactivity Disorder (ADHD) and Non-ADHD Adolescents: Evidence for Gateway Drug Effects

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Introduction

The purpose of this review is to discuss the characteristics of nicotine and cannabis that make them potential gateway drugs to young people. There is substantial evidence that indicates nicotine and cannabis influence experimentation with "harder" drugs that adolescents have a tendency to abuse. I have reviewed the literature as it pertains to ADHD adolescents because it is well documented that ADHD kids have problems with judgment, impulsivity and may seek recreational drugs as an attempt to improve their attention or help them cope with the emotional distress associated with ADHD life. There are many studies that show non-ADHD adolescents, whose brains develop slowly and in specific ways, are vulnerable to the effects of drugs such as nicotine and cannabis. In this review, discussion of drug effects ranges from psychological, behavioral, physiological, developmental and neurological at the systems and molecular level.

In 2011-2013, 9.5% percent of children aged 4-17 years of age have been diagnosed with ADHD at some point in their youth [1]. For children aged 12-17, ages that are at great risk for experimenting with drugs of abuse, 11.8% have been diagnosed with ADHD [1]. A majority of cigarette smokers begin using tobacco during adolescence. Approximately 75% of adult tobacco users report that their first tobacco use occurred 11-17 years of age and 60% before 14 years of age [2]. Adolescent smokers develop greater cigarette dependence and higher rates of smoking throughout adult life [2]. It is clear that Attention Deficit Hyperactivity Disorder (ADHD) children are at greater risk for substance use than non-ADHD kids [3]. It's been estimated 53% of individuals in the United States have used cannabis by age 25 years [4]. Nicotine and cannabis seem to open the door for using additional drugs. Nicotine and cannabis promote use of additional drugs psychologically by increasing curiosity and lowering perception of risk and/or by priming the brain physiologically through molecular alterations in the reward system, dopamine activity and the Dopamine Transporter (DAT) [5,6].

How does Nicotine act as a Gateway Drug?

Kandel and Kandel [5] have compared drug use and addiction as a form of memory, as such they designed animal studies to elucidate the molecular changes that take place as part of nicotine driven Gateway process. Several brain regions have been established as key areas involved with drugs of abuse and addiction. One of those areas is the striatum. Activation of Cyclic AMP response-element-binding protein (CREB) is key towards converting short-term memory to long-term memory. CREB activation appears to be involved in drug addiction. Activation of CREB is joined with downstream transcription of target genes FosB and Delta FosB. Delta FosB accumulation in the striatum is integral to developing drug addiction markers in the striatum. The Kandels used conditioned place preference and locomotor sensitization, two reliable behavioral techniques for identifying addiction behaviors and drug-drug sequences. They found priming mice for 7 days with nicotine and then giving 4 days of co-administered nicotine and cocaine, caused significant increases in activity [5]. This treatment also caused mice to significantly increase their place preference, a sensitive measure of addictive drug activity and reward system changes. It has been shown that nicotine influences cocaine use. Predosing mice with nicotine changed the response to cocaine dramatically. Reducing excitatory input to the nucleus accumbens lowers inhibitory output from the nucleus accumbens to the ventral tegmental area [5,6]. This may promote disinhibition in this circuit, producing more dopamine, which in turn may promote rewarding effects of abuse drugs. Thus, nicotine may reduce excitatory drive into nucleus accumbens. It is clear that behavioral changes to drugs and drug addiction are preceded in part by changes in molecular substrates that involve the reward pathway and dopamine [5-9].

How does Cannabis act as a Gateway Drug?

Batalla et al. [10] determined cannabis exposure alters the normal relationship between Dopamine Transporter 1 (DAT1) polymorphism and the anatomy of total and subregional hippocampal volumes, and that specific hippocampal subregions may be particularly affected. Cannabis has also been shown to alter short term hippocampal dependent object-

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recognition memory, via alterations in protein kinase C expression [11]. It is important to clarify when discussing the cannabis gateway effect, neurocognitive effects and any aspect of addiction; we are focusing on the role of Delta-9-Tetra-Hydro-Cannabinol (delta-9-THC), the psychoactive component and not the effects caused by a myriad of cannabinoids found in cannabis, independent of THC. First, some define a gateway drug as a drug that lowers the addiction threshold for another drug. It has already been shown that adolescent cannabis users are more likely to try and become addicted to prescription opioid drugs such as OxyContin [12]. In this study, using cannabis lowed the addiction threshold of a second drug, OxyContin. Cerda et al. have shown that once kids become addicted to OxyContin, they often transit to a less expensive, easier to find but very dangerous drug like heroin [13]. There is evidence that an adolescent's social milieu or peer influences are associated with gateway drug experimentation [14]. It is important to understand adolescents have various motivations to try and to continue using drugs. First, ADHD and non-ADHD kids may be seeking a way to improve performance in school and other interests. Attempting to improve performance can be a primary motivator. Second, kids may discover a drug such as cannabis or nicotine makes them feel better. Third, kid's motivation to continue using drugs can become great, once they are addicted. This is especially true when cannabis use leads to opioids such as OxyContin or heroin. Camargo et al. collected inventories from ADHD subjects in a rehabilitation facility and compared age of first contact with drugs of abuse including cannabis and cocaine. They also looked at the likelihood of subsequent cocaine use and severity of dependence. One central premise to this and other ADHD drug dependence studies is that there is a failure of behavioral inhibition that leads to hyperactivity, inattention, distraction and impulsivity [15]. Investigators found that cocaine dependence was greater than that of cannabis. Here, the age of first cocaine use was lower among the ADHD population than other groups undergoing rehab. ADHD patients in rehab overrepresented ADHD patients found in the general population [15]. Age of first use for cannabis correlated with age of facility admission, as well as frequency of ADHD symptoms. First, cannabis use was associated with younger patients.This observation has been made previously with cocaine [16], where cocaine dependent individuals in rehab were much more likely to have ADHD. Upadhyaya et al. found that the number of ADHD symptoms correlated with cannabis, tobacco and alcohol use [17]. It has also been shown that self-reported ADHD is significantly associated with younger initiation of alcohol, cigarettes, cannabis, nasal cocaine, injected cocaine with an elevated use of nasal and injected heroin [18]. Carroll and Rounsaville found that patients with ADHD are admitted for treatment for cocaine dependence earlier and also found heavier cocaine use in patients with ADHD [19]. Greater use and heavier consumption of cannabis in college ADHD students appears related to younger first use [20]. Another study concluded adolescent cannabis is a potential risk factor for subsequent cigarette smoking, which leads to nicotine addiction. In this study, investigators found the risk was primarily for women [21]. College students in Latin America show a definite pattern to their drug use. Investigators studied different drugs, including cannabis, alcohol, cocaine, prescription opioids, and tranquilizers, there is a definite sequence to the drug sampling and use. Cannabis use precedes cocaine initiation, prescription opioids, non-medical tranquilizers and even alcohol [22]. It is clear that kids with ADHD are vulnerable to recreational drugs that are potentially harmful and addictive. But what about the stimulant and non-stimulant medications many ADHD kids may take? What effects do mixed amphetamine salts such as extended release (MAS-XR) have on ADHD cannabis and cocaine use? Notzon et al. [23] report that MAS-XR treatment is associated with weekly cannabis abstinence, thus amphetamine salts do reduce cannabis intake. However, the non-stimulant ADHD drug atomoxetine failed to affect marijuana abuse in an ADHD population. Another study found kids who start drinking before age 15 are significantly more likely to start a cannabis habit as they age. The authors also associated early alcohol use with psychiatric disorders [24]. Cannabis addiction presents a serious problem to many young people. However 9.1 % of the Adult US population reports having resolved a substance use problem earlier in their life, with 10.97% of those being cannabis [25]. Taylor et al. provide yet more data that show adolescents (one in five) who smoke cannabis occasionally or regularly progress to harmful drug habits early in adulthood, such as nicotine, alcohol or other illicit drugs [26]. Conduct/oppositional problems in childhood and attention problems in adolescence predicted cannabis use in their young adult years (25 yrs) [27]. It is critical to consider the role of peers, in drug experimentation and progression to dangerous drugs. Creating a drug friendly environment or an environment that fosters drug curiosity and experimentation can be critical to first time drug experimentation or progressing to addictive drugs.In this vein, Otten et al. [28] have shown that kids who seek drug using friends or foster relationships with kids that are already taking drugs, are more likely to try or progress towards harmful drugs themselves.

Neurocognitive and Health Consequences of Using Adolescent Nicotine and Cannabis Use.

While understanding factors that may contribute to the gateway phenomena, and the drugs that may be most relevant to ADHD, it is important to remember there are serious neurocognitive and health consequences to cannabis and nicotine use. Synaptic pruning is a dynamic process that helps determine cortical volume. Synaptic pruning maintains optimal cortical volume, especially during developmental periods and late-life aging. Inadequate pruning may contribute to pathology in schizophrenia and Alzheimer's disease, for example [29-31]. Many studies report an association between cannabis use and changes in cortical thickness which can be considered similar to cortical volume. In adolescent and young adult heavy cannabis users, Jacobus and colleagues found that cortical thickness was abnormal [32]. In a longer-term study of 18, 19 and 21 year olds, cannabis users had thicker estimates in widespread brain regions by follow-up (~age 21). These findings also suggested positive correlations between cortical thickness and lifetime cannabis use [33]. When Orbitofrontal (OFC) and caudate volumes from dependent and non-dependent cannabis users are compared in a multi-site study, no difference was observed between pooled dependent and non-dependent groups vs healthy controls. However, when cannabis dependent vs cannabis non-dependent groups were compared, medial and lateral OFC volumes were significantly smaller in the cannabis dependent group. Reduced OFC volumes were associated with higher monthly cannabis intake [34]. Cannabis use has also been associated with differences in functional imaging activation especially in hippocampal, prefrontal and cerebellar areas. Additional support for cannabis induced changes in neural architecture, comes from findings that there are structural differences in the orbitofrontal region and the hippocampus [35]. Emerging adulthood (18-25 years old) is regarded as a time of identity exploration that includes a peak in risky behaviors, such as substance use and misuse. ADHD is also associated with greater levels of risky behaviors. There is evidence connecting adolescent ADHD impulsivity to substance abuse [2]. Among the many health concerns for adolescents is the observation that cannabis use is associated with greater Body Mass Index (BMI) and increased likelihood of becoming obese. This effect is independent of alcohol and nicotine use, depression, parent education, gender, race or ethnicity [36]. Until recently, it has been argued that offspring are not influenced by parental use of cannabis. However, Szutorisz and colleagues [37] have shown, that adult mice exposed to THC generate offspring that have an altered threshold for heroin seeking. Thus, compared to controls, these animals exert significantly greater effort to obtain heroin. Extrapolating to humans, kids that are conceived by cannabis consuming parents, may be more likely to become heroin addicts. The incidence of stroke in young, healthy adults whose only risk factor is cannabis use, has been growing alarmingly in recent years [38]. It is not unusual for a cannabis user, especially heavy user, to report feelings of paranoia at times. Freeman et al. [39] sought to identify and evaluate cognitive mechanisms that may account for this paranoia. They infused IV THC into volunteers and found THC significantly increased paranoia, negative affect such as anxiety, worry, depression, and negative thoughts about the self. THC also caused a range of anomalous experiences, and reduced working memory capacity, although working memory changes did

not cause paranoia. The increase in negative affect and in anomalous experiences fully accounted for the increase in paranoia. The authors state making subjects aware of potential THC effects did not change their experience. The most likely mechanism of action causing paranoia was the generation of negative affect and anomalous experiences [39]. There has been much interest in the effect of cannabis on cognitive domains, including IQ and working memory. The data are mixed to date. In a study of lifetime cannabis user who are also younger than 25 yrs with psychotic disorders, it has been shown that cannabis use is associated with worse performance on IQ, verbal working memory and motor inhibition [40]. Pauselli et al. [41] looked at the relationship between age of cigarette initiation, subsequent cannabis use and first episode of psychosis. They found there was an association between cannabis use, age of first episode psychosis and likelihood for a negative outcome of a first episode. While it would be convenient to characterize the young cannabis user as a mellow person, happy to stretch out on the couch with a carton of ice cream, bag of Doritos and a movie, this not a true representation of all cannabis users. Cannabis disinhibits brain circuitry at a neuronal level, and at the behavioral level. A disinhibited people with natural violent tendencies, have been show to act on their violent tendencies, under the influence of cannabis. They are also more likely to have impaired judgement. Young males from the Cambridge Study of Delinquent Development were followed up between the ages of 8 and 56 years to investigate the association between cannabis use and violence. In this population, there is strong evidence cannabis use predicts subsequent violence [42].

NIDA's Dr. Marylin Huestis Warns of Adverse Cognitive Effects of Marijuana; Some Therapeutic Uses Seen

"THC binds to cannabinoid receptors throughout the brain and affects all aspects of brain function, including executive function (paying attention, memory and learning, decision-making); emotion, coordination and motor control, appetite and pain sensation. Smoking or inhaling marijuana sends a concentrated dose into the lungs and quickly releases THC into the brain, causing a rapid onset of effects". Recent surveys show that the perceived danger of using marijuana is down among adolescents. Yet studies reveal that marijuana negatively affects brain development and is associated with decreased IQ, especially in kids who start using pot when they're younger than 15." Huestis said persistent marijuana use from childhood to middle age can cause significant neurological decline [43]. Studies show conflicting results about lasting cognitive impairments from marijuana use. In some studies, the heaviest users have irreversible loss of cognitive performance. Other studies show impairment for more than a week but then cognitive function improved or returned to normal after a month. In a recent NIDA-NIMH collaborative study of infrequent marijuana smokers, THC could be found in the blood a month later in some participants. If THC can remain in the body after 30 days of abstinence, "This creates a huge problem with driving under the influence," said Huestis. Multi-site studies over the past decade have shown an increased risk of car crashes if THC is at all measurable in the body [43].

In this review, I have covered the use of nicotine, cannabis in adolescents with and without ADHD and their influences on potentially harmful drugs such as cocaine, OxyContin, heroin and alcohol. I have defined the gateway drug, and provided examples of how nicotine and cannabis promote use of other dangerous drugs at a molecular level and consequential reward system changes, such as dopamine alterations in the striatum, and the role of social influences. These aspects of the gateway phenomena have been summarized elsewhere [5,6,44,45]. Perhaps the most shocking evidence of a gateway drug effect with cannabis, are the data from Yale University that show kids who smoke cannabis are more likely to become addicted to OxyContin. That study is followed up by a study that clearly shows non-prescription opioid use, such as OxyContin, leads to a transition to heroin, in part because heroin is cheaper and easier to obtain. This review also summarizes many consequences of nicotine and cannabis use in adolescents. Adolescents and ADHD kids are vulnerable to the effects of cannabis in part due to their prolonged neurodevelopment. Some believe the prefrontal cortex is particularly susceptible to drugs of abuse, for this very reason. While I have provided evidence that cannabis use alters the brain's neural architecture, such as cortical thickness, I have reviewed data which indicates young healthy people, with no stroke risk factors, are showing a substantial uptick in strokes, while using cannabis [38]. Mental health issues including first episode psychosis are serious concerns [39-41]. There is evidence that people with violent tendencies will become violent while using cannabis, presumably through an ability to cause disinhibition.There are many studies which conclude cannabis impairs several aspects of cognition, however additional studies are needed to clarify effects on memory vs attention vs other cognitive measures [43]. The evidence that cannabis interferes with sensory-motor processing is growing, and this is borne out by increases in traffic accidents and fatalities [43]. For review of consequences and potential solutions to the harmful effects of THC, see Brucato [46]. I have focused primarily on the negative consequences of cannabis use, and its position as a gateway drug. There is a strong bias today, towards legalizing and using recreational cannabis. This bias is sharply juxtaposed against a plethora of data indicating cannabis produces harmful effects to adolescents, with or without ADHD. The high concentration of THC found in today's cannabis can do damage to the adolescent brain. I have not mentioned medical marijuana, because it is not relevant to this discussion. The possibility that medicinal cannabis may provide some therapeutic benefit to certain populations does not invalidate the legitimate concerns about cannabis/THC and the harm done to adolescents. A responsible community must find ways to protect kids, acknowledge negative data and the risks posed to users, in light of popularity and pressures to legalize. We must make decisions about cannabis policy, medicinal potential, long term economic influence, and the individual's personal desire to use recreational drugs like cannabis. Well documented harmful effects on adolescents cannot be overlooked in this process.

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