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

Rick Brucato*
Cascade Chemical Biology, Princeton Corporate Plaza, USA

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 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-
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. Synthetic pruning is a dynamic process that helps determine cortical volume. Synthetic pruning maintains optimal cortical volume by pruning neural connections and synaptic pruning facilitates changes in neural architecture, controlling 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, Jacobs 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 the brain matures, it maintains cortical volume and changes in volume 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, coming 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 exhibit 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 improvement 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 substances such as cocaine, OxyContin 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.

**References**

1. Pastor P, Reuben C, Duran C, Hawkins L. Association between diagnosed ADHD and selected characteristics among children aged 4-17 years: United States, 2011-2013. NCHS Data Brief. 2015 May;201.
2. Levin ED, Slade S, Wells C, Cauley M, Petro MA, et al. Threshold of Adulthood for the Onset of Nicotine Self-Administration in Male and Female Rats. Behav Brain Res. 2011 Dec;225(2):473-481.
3. Egan TE, Dawson AE, Wymb HS. Substances used in Undergraduate Students with Histories of Attention-Deficit-Hyperactivity-Disorder (ADHD): The Role of Impulsivity. Subst Use Misuse. 2017 Aug;52(10):1375-1386.
4. Lee JY, Brook JS, De La Rosa M, Kim Y, Brook DW. The association between alcohol use trajectories from adolescence to adulthood and cannabis use disorder in adulthood: a 22-year longitudinal study. Am J Drug Alcohol Abuse. 2017 Nov;43(6):727-733.
5. Kandel E, Kandel D. Molecular basis for nicotine as a gateway drug. N Engl J Med. 2014 Sep;371(10):932-943.
6. Kandel D, Kandel E. The gateway hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatr. 2015 Feb;104:130-137.
7. Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci. 2(10):695-703.
8. Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci. 2006;29:565.
9. Nestler EJ, Malenka RC. The addicted brain. Sci Am. 2004 Mar;290:78-85.
10. Batalla A, Lorenzetti V, Chye Y, Yucl Y, Soria-Casas C, et al. The influence of DAT1, COMT, and BDNF genetic polymorphisms on cocaine and cannabis use disorder in adulthood: a 22-year longitudinal study. Am J Drug Alcohol Abuse. 2017 Nov;43(6):727-733.
11. Busquets-Garcia A, Gomis-Gonzalez M, Salgado-Mendiellada V, Galera-Lopez L, Puigermann E. Hippocampal protein kinase C signaling mediates the short-term memory impairment induced...
by delta-9-tetrahydrocannabinol. Neuropsychopharmacology. 2018 Apr;43(5):1021-1031.

12. Fiellin LE, Tetault JM, Becker WC, Fiellin DA, Hoff RA. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. J Adolesc Health. 2013 Feb;52(2):158-163.

13. Cerda M, Santalla J, Marshall BD, Kim JH, Martins SS. Nonmedical prescription opioid use in childhood and early adolescence predicts transitions to heroin use in young adulthood: a national study. J Pediatr. 2015 Sep;167(3):605-612.

14. Otten R, Mun CJ, Dishion TJ. The social exigencies of the gateway progression to the use of illicit drugs from adolescence into adulthood. Addict Behav. 2017 Oct;73:144-150.

15. Camargo CH, Dornelles TF, Barszcz K, Martins EA. Attention deficit hyperactivity disorder and drug addiction rehabilitation patients. Arq Neuropsiquiatr. 2016 Dec;74(12):1003-1007.

16. Ballon N, Brunault P, Cortese S. Sensation seeking and cocaine dependence in adults with reported childhood ADHD. J Atten Disord. 2015;19(4):335-342.

17. Upadhyaya HP, Carpenter MJ. Is attention deficit hyperactivity disorder (ADHD) symptom severity associated with tobacco use? Am J Addict. 2008 May-Jun;17(3):195-198.

18. Dunne EM, Hearn LE, Rose JJ, Latimer WW. ADHD as a risk factor for early onset and heightened adult problem severity of illicit substance use: an accelerated gateway model. Addict Behav. 2014 Dec;39(12):1755-1758.

19. Carroll KM, Rounsaville BJ. History and significance of childhood attention deficit disorder treatment in forest. Sensing-seeking cocaine abusers. Compr Psychiatry. 1993 Mar-Apr;34(2):75-82.

20. Bidwell LC, Henry EA, Willcutt EG, Kinnear MK, Ito TA. Childhood and current ADHD symptom dimensions are associated with more severe cannabis outcomes in college students. Drug Alcohol Depend. 2014 Feb;135:88-94.

21. Nguyen TQ, Ehnessajjad C, Stuart EA, Kennedy RD, Johnson RM. Does Marijuana use at ages 16-18 predict initiation of daily cigarette smoking in late adolescence and early adulthood and early adulthood? A propensity score analysis of ADD health data. Prev Sci 2018 Feb.

22. Castaldelli-Maia JM, Nicastri S, Cerda M, Kim JH, de Oliveira LG. In-transition culture of experimentation with cannabis in Latin American college students: A new role within a potential drug use sequencing pattern. Alcohol Rev. 2018 Feb;37(2):273-281.

23. Notzon DP, Mariani JJ, Pavlova M, Glass A, Mahony AL, et al. Mixed-amphetamine salts increase abstinence from marijuana in patients with co-occurring Attention-Deficit/Hyperactivity Disorder and cocaine dependence. Am J Addict. 2016 Dec;25(8):666-672.

24. Tanaree A, Assanangkornchai S, Kitttrattanapanboon P. Pattern and risk of developing alcohol use disorders, illegal substance use and psychiatric disorders after early onset of alcohol use: Results of the Thai National Mental Health Survey 2013. Drug Alcohol Depend. 2017 Jan;170:102-111.

25. Kelly JF, Greene MC, Bergman BG. Is recovery from cannabis use problems different from alcohol and other drugs? Results from a national probability-based sample of the United States adult population. Int J Drug Policy. 2018 Mar;53:55-64.

26. Taylor M, Collin SM, Munro MR, MacLeod J, Hickman M, et al. Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: findings from a UK birth cohort. J Epidemiol Community Health. 2017 Aug;71(8):764-770.

27. Zohsel K, Baldus C, Schmidt MH, Esser G, Banaschewski. Predicting later problematic cannabis use from psychopathological symptoms during childhood and adolescence: Results of a 25-year longitudinal study. Drug Alcohol Depend. 2016 Jun;163:251-255.

28. Otten R, Mun CJ, Dishion TJ. The social exigencies of the gateway progression to the use of illicit drugs from adolescence into adulthood. Addict Behav. 2017 Oct;73:144-150.

29. Stevens B, Allen NJ, Vasquez LE, Howell GR, Christopherson KS, et al. The classical complement cascade mediates CNS synapse elimination. Cell. 2007 Dec;131(6):1164-1178.

30. Hong S, Beja-Glasser VE, Nfonoyim BM, Frouin A, Li S. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science. 2016 May;352(626):712-716.

31. Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, et al. Schizophrenia risk from complex variation of complement component. Nature. 2016 Feb;530(7589):177-183.

32. Jacobus J, Castro N, Squeglia LM, Meloy MJ, Brumbach T. Adolescent cortical thickness pre- and post-marijuana and alcohol initiation. Neurotoxicol Teratol. 2016 Sep-Oct;57:20-29.

33. Jacobus J, Squeglia LM, Meruelo AD, Castro N, Brumbach T, et al. Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood. Dev Cogn Neurosci. 2015 Dec;16:101-109.

34. Chye Y, Solowij N, Suo C, Batalla A, Cousijn J, et al. Orbitofrontal and caudate volumes in cannabis users: a multi-site mega-analysis comparing dependent versus non-dependent users. Psychopharmacology (Berl). 2017 Jul;234(13):1985-1995.

35. Ganzer F, Broning S, Kraft S, Sack PM, Thomasius R. Weighing the evidence: a systematic review on long-term neurocognitive effects of cannabis use in abstinent adolescents and adults. Neuropsychol Rev. Jun;26(2):186-222.

36. Ross JM, Graziano P, Pacheco-Colón I, Coxe S, Gonzalez R. Decision-making does not moderate the association between cannabis use and body mass index among adolescent cannabis users. J Int Neuropsychol Soc. 2016 Oct;22(9):944-949.

37. Szafter Z, Di Neri JA, Sweet E, Egervari G, Michaelides M, et al. Parental THC exposure leads to compulsive heroine-seeking and altered striatal synaptic plasticity in the subsequent generation. Neuropsychopharmacology. 2014 May;39(6):1315-1323.

38. Hemachandra D, McKeitn R, Cherbuin N, Anstey KJ. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. Aust N Z J Public Health. 2016 Jun;40(3):226-230.

39. Freeman D, Dunn G, Murray RM, Evans N, Lister R. How cannabis causes paranoia: using the intravenous administration of Δ9-tetrahydrocannabinol (THC) to identify key cognitive mechanisms leading to paranoia. Schizophr Bull. 2015 Mar;41(2):391-9.

40. Bogaty SER, Lee RSC, Hickie IB, Hermens DF. Meta-analysis of neurocognition in young psychosis patients with current cannabis use. J Psychiatr Res. 2018 Jan;99:22-32.

41. Pauselli L, Birnbaum ML, Vázquez Jaime BP, Paolini E, Kelley ME. Demographic and socioenvironmental predictors of prefrontal cannabis use among patients with first-episode psychosis. Schizophr Res. 2018 Jan;90920-99641830042-2.

42. Schoeler T, Theohald D, Pingault JB, Farrington DP, Jennings WG. Continuity of cannabis use and violent offending over the lifetime course. Psychol Med. 2016 Jun;46(8):1663-1677.

43. Steinberg D. NIDA's Huestis Warns of Adverse Cognitive Effects of Marijuana; Some Therapeutic Uses Seen. NIH record. 2014 August 15;Vol. LXVI, No. 17.

44. De Luca MA, DiChiara G, Cadoni C, Lecca D, Orsolini L, et al. Cannabis, epidemiological, neurobiological and psychopathological issues: an update. CNS Neurol Disord Drug Targets. 2017;6(5):598-609.

45. Kollins SH, Adcock RA. ADHD, altered dopamine neurotransmission, and disrupted reinforcement processes: implications for smoking and nicotine dependence. Prog Neuropsychopharmacol Biol Psychiatry. 2014 Jul;52:70-78.

46. Brucato R. Current data raises toxicity and safety concerns about today’s high THC content cannabis. MOJ Toxicol. 2017 Mar;3(1):00045.