Journal of
Addiction Research & Therapy
ISSN: 2155-6105

Oberbarnscheidt and Miller, J Addict Res Ther
2017, S11:016
DOI: 10.4172/2155-6105.1000S11-016

Research Article OMICS International

Marijuana's Role in The Adolescent Population

Thersilla Oberbarnscheidt* **and Norman S Miller**

[1]*Department of Psychiatry, Central Michigan University, USA*

[2]*CEO of Health Advocates PLLC, East Lansing, MI, Clinical Professor of Psychiatry, Department of Psychiatry, Medical College of George, Augusta University, Augusta, Georgia, USA*

***Corresponding author:** Thersilla Oberbarnscheidt, Department of Psychiatry, Central Michigan University, USA; E-mail: Oberb1t@cmich.edu

Received date: January 10, 2017; **Accepted date:** February 02, 2017; **Published date:** February 09, 2017

Abstract

Marijuana is the most commonly used illicit substance in the United States and worldwide. The smoking of marijuana is an increasingly observed phenomenon in the adolescent population and even more common nowadays than cigarette smoking. A special focus should therefore aim to the effects of marijuana in that particular age group.

Adolescents are particularly vulnerable to the effects of marijuana because their brain and neuro-circuits are still developing. The exposure of marijuana to the still pruning brain causes not only short-term cognitive impairment but also permanent, life-long reduction in their cognitive abilities. This is due to marijuana's effect on processing speed and a reduction in gray matter in several brain regions as well as a decrease in white matter.

Marijuana is viewed as a "gateway" drug and more so than adults, the adolescents are at higher risk to develop a subsequent drug addiction after the exposure to marijuana. A positive correlation between the age of first exposure to marijuana and the development for an addiction to other drugs has been shown. There is also a strong association between the onset of other psychiatric disorders, for example bipolar disorder, psychosis, depression and anxiety and even suicidal ideations in context with the use of marijuana.

This article is based on a review of the current scientific literature with the aim to focus on the indications, outcomes, toxic effects and pathological evidence from the use of marijuana in the adolescents.

Keywords: Marijuana; Bipolar disorder; Psychiatry; *Cannabis sativa*

Introduction

The use of marijuana as the "natural" form of cannabis goes back to ancient years but is an increasing problem, particularly in the adolescent population [1,2] since this is the age group when the initial introduction to marijuana most likely occurs [3-6].

Marijuana is a mixture of dried seeds, stems, leaves, and the flowering tops of the plant *Cannabis sativa* [6-8]. Marijuana is a Schedule I controlled substance by the United States Drug Enforcement Agency (DEA) and is therefore illegal in the US.

Substances in this class have no accepted medical use in the United States under US Federal law [9]. The use of marijuana as a medicine is subject to vivid discussion and a part of the US population would prefer to be legalized as a medication instead of a drug. Unfortunately, the discussion is often times not guided by research evidenced-based data.

For the smoked, natural form of Marijuana with its 460 chemical components, there is no FDA approved indication due to varying levels of contents, toxicity and potential of addiction to the drug [6,8,9]. The pharmacology of marijuana with the high degree of toxicity and redistribution into the blood stream long after last use makes it a very dangerous and unpredictable drug [3,4].

While some users have relatively benign experiences with marijuana, others develop physical dependence and addiction [5,10].

The withdrawal from marijuana leads to the Marijuana abstinence syndrome and consists of anxiety, depression, irritability and insomnia [3,4].

The use of marijuana in the adolescent also becomes more dangerous through the current trend is to breed higher potency marijuana with a stronger content of THC. The average potency of the delta-9-tetrahydrocannabinol (THC) increased from 3% in 1992 to 11% in 2010 [1].

The adolescents are particularly at high risk of marijuana related toxic effects. Their neurological system is developing and more vulnerable to the psychoactive and toxic effects of marijuana [3].

Methods

This article is based on a review of current scientific literature. Databases used for acquiring the journal articles were PubMed, Ovid, Cochrane Library, CINAHL Plus. Keywords used for the search were: Marijuana, cannabis, Marijuana in adolescents, marijuana in teenagers, Marijuana in children, drug use among adolescents, comorbidities and marijuana, academic performance and marijuana, ADHD and marijuana, Depression and Marijuana, crime associated with marijuana in adolescents. Additional public databases that were consulted to acquire information were: DEA, DSM V, NIH, White House office of national drug control.

Results

Patterns of marijuana use in the adolescent

Marijuana initiation typically occurs during the adolescence. The majority of adolescents start experimenting with drugs in their teenage years [11].

Given the classification as a Schedule I substance and no FDA approval for any medical condition there is lack of evidence to treat any medical condition with marijuana [9]. However the adolescent age group easily gets mislead by the term "Medical Marijuana" which may imply some "benefit" for medical conditions. The term "natural" easily is misinterpreted with "harmless".

The use of Marijuana currently exceeds the tobacco smoking in adolescents in the US [12]. According to the "Monitoring the future survey" from 2012, roughly half of the high school seniors have tried marijuana, 23% are current users, and 7% use marijuana daily [13]. Males are more likely to experience opportunities to use but then there is no gender difference regarding the continuation of the use [13]. Also, adolescents with tendencies to aggressive behaviors are more likely to have the opportunity to use, but overall every adolescent is at risk for the initiation of marijuana use, not limited to low socio-economic status and low-income families.

Particularly younger users are prone to develop dependence symptoms and addiction. The younger the age onset of the use of marijuana, the greater the risk for the development of addiction and dependence. The physical dependence to marijuana in the adolescents leads to the development of withdrawal symptoms while the addiction is defined by the compulsive use of marijuana (Chart 1).

Cannabis Use (Marijuana Use) Disorders According to DSM V	
Consequence	**Definition/Symptoms**
Cannabis Use Disorder	A problematic pattern of cannabis use leading to clinically significant impairment or distress as manifested by at least two of the following occurring in a 12 month period:
	1. Cannabis is often taken in larger amounts over a longer period than was intended.
	2. There is a persistent desire or insignificant effort to cut down or control cannabis use.
	3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
	4. Craving or a strong desire or urge to use cannabis.
	5. Recurrent cannabis use resulting in failure to fulfill major role obligations at work, school, or home.
	6. Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
	7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use.
	8. Recurrent cannabis use in situations which is physically hazardous.
	9. Cannabis use is continued despite knowledge of having persistent or recurrent physical or psychological problems that are unlikely to have been caused or exacerbated by cannabis.
	10. Tolerance, as defined by either:
	a) A need for markedly increased amounts of cannabis to achieve intoxication and desired effect, or
	b) A markedly diminished effect with continued use of the same amount of cannabis.
	11. Withdrawal, as manifested by either:
	a) The characteristic withdrawal symptoms for cannabis, or
	b) A closer related substance is taken to relieve or avoid withdrawal symptoms.
Cannabis Intoxication	1.Recent use of cannabis
	2. Clinically significant problematic behavior or psychological changes (e.g. impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal) that develop during, or shortly after, cannabis use
	3. Two or more of the following signs or symptoms developing within two hours of cannabis use:
	a) Conjunctival injection
	b) Increased appetite
	c) Dry mouth

	d) Tachycardia
	4. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.
Cannabis Withdrawal	1. Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily over a period of at least a few months)
	2. Three or more of the following signs and symptoms develop within approximately one week after cessation of heavy, prolonged use:
	a) Irritability, anger or aggression
	b) Nervousness or anxiety
	c) Sleep difficulty (e.g. insomnia, disturbing dreams)
	d) Decreased appetite or weight loss
	e) Restlessness
	f) Depressed mood
	g) At least one of the following physical symptoms causing significant discomfort:
	i) Abdominal pain,
	ii) Shakiness/tremors,
	iii) Sweating,
	iv) Fever,
	v) Chills
	vi) Headache
	3. The signs or symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
	4. The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Chart 1: The criteria for addiction are clearly defined in the DSM V.

A study interviewed 164 students age 14-18, showed that 74% of adolescents interviewed had used some else's medical marijuana card [4].

The effects of marijuana on the adolescent brain

The adolescent brain is more vulnerable to the toxic effects of marijuana and the acute and chronic effects resulting from the use of marijuana are a great public health concern [14].

The adolescent brain is still undergoing neurodevelopmental changes in brain regions responsible for higher-order thinking and executive functioning, especially in the pre-frontal and parietal cortex [15]. Cranial pruning occurs into the mid 20's and development of quality and volume of white matter continues into the early 30's [15]. This on-going neuro-cognitive development makes the brain more sensitive and vulnerable for toxic substances as marijuana is.

The use of marijuana is associated with negative outcomes in the adolescent's development regarding their academic performance, cognitive as well as behavioral and psychiatric development. The use of marijuana further leads to decreased socio-economic functioning including higher drop off rates from schools, higher unemployment rates and lower income.

The exposure to marijuana early in life and psychiatric illnesses

Research documented that marijuana use in adolescents predisposes the marijuana user to motivational, affective and psychotic disorders [16].

Marijuana increases the likelihood of a drug addiction in adulthood and also produces long-lasting effects on anxiety and mood and thought disorders.

The manifestation of psychiatric illnesses occurs most frequently in the adolescent (about 40%) and 25% in adults [17]. This makes the use of marijuana even more dangerous and risky in terms of increasing the vulnerability.

Depression and suicidality

Adolescent marijuana users frequently claim depression as a reason for use and self-medication. Against that believe, studies have shown that marijuana increases the feelings of depression. This misperception in the user might be related to the temporary euphoria or feeling "stoned" or "numbed" when intoxicated followed by a feeling of more severe depression.

In addition, marijuana increases the suicidality among adolescents. A longitudinal study showed that adolescents who are exposed to marijuana have an increased risk for suicidal ideations and a higher rate of suicide attempts [18].

Some studies show contrary data and don't confirm the negative influence of marijuana on the adolescent's mood. One study showed no difference regarding the degree of adolescent's depression, anxiety as well as suicidal ideations or suicide age compared to the non-using control group, but by early adulthood the adults with a history of marijuana used had a significantly higher incidence of suicidal ideation and suicide attempts [18]. Other studies confirmed the finding of greater rates of depression in marijuana users versus non-users [19].

Psychosis

The use of marijuana causes psychosis as one of the toxic effects but in addition it increases the risk of developing schizophrenia or schizoaffective disorders in the adolescents. Adolescents who are genetically predisposed to develop schizophrenia, the disease can manifest earlier and more fulminant if marijuana is used [20].

Case control studies and cohort studies have shown that the odds-ratio between the use of marijuana and the development of psychosis is 1.41 for occasional users and 2.09 for frequent users [21]. Statistically this means that an odds-ratio above 1 means that there is an association between the 2 variables.

Furthermore the use of marijuana in early life increases the risk to develop schizotypal or schizophreniform personality disorder and the adult symptomatology with this disorder [22].

Addiction

Marijuana is the most commonly used illicit substance in the United States and worldwide (1). Because of its availability, marijuana is often the "gateway drug" and leads to the consecutive use of other illicit substances [23].

A cohort study performed by Kandel conducted on High school students. Over a quarter of those students who progressed to illicit drug use (i.e., heroin, amphetamines, and LSD) had a previous experience with marijuana while only 2-3% of legal drug users without marijuana experiences progressed to the use of illicit substances [24].

Another study demonstrated as well that early marijuana use in adolescents predisposed them to the use of cocaine and alcohol over a 1 year period [25].

In a large Canadian survey of 2500 adolescents, 30% used marijuana, and 35% of the marijuana users reported at least one criterion for marijuana dependence, such as withdrawal (17%) or continued use despite health problems (13%) [26].

A frequently cited study in literature from New Zealand following a cohort group for 25 years, confirmed the same observation that early exposure to marijuana causes an increased risk for subsequent drug use and dependence later in life. The group showed a positive correlation for age and the development of an addiction to other drugs or dependence. The earlier the exposure to marijuana in life occurs, the higher the risk for the development of an addiction. The development of drug use and dependence declines with increasing age of initiation [27].

These findings have also been observed in animal studies utilizing adolescent rats. The exposure to Marijuana increased the rate of heroin self-administration in one model [28].

Further investigation in the pathophysiology for the development of the marijuana dependence in this rat model showed that marijuana and in particular the THC content increased the inhibitory G-protein coupled signaling in the rodent midbrain which is affecting the dopaminergic projections and enhances the mesolimbic dopamine, which leads to an enhanced reward [29].

Cognition and attention

The exposure of marijuana in the adolescent has negative effects on their cognition and attention. The intoxicating effects of marijuana cause difficulties with attention, problem solving as well as impairment in judgment, decision-making, and learning [30].

The toxic effects on cognition are leading to an acute impairment while using which lasts for about 6 h. However the cognitive decline and impairment might be longer lasting or even permanent in adolescents who use marijuana regularly [31]. A prospective cohort study of more than 1000 individuals found that those who used marijuana regularly in their teen years had persistent cognitive decline that did not resolve with cessation [32].

The degree of cognitive impairment resulting from marijuana use is the more severe the earlier the use of marijuana was initiated and the more marijuana was used [32]. Another large, long-term study from New Zealand, following 1000 adolescents from age 13 through 38, found a severe cognitive decline. The study showed that teenagers smoking marijuana heavily had on average an 8-point decline in their IQ over time [27].

A common phenomenon among the marijuana users is a discrepancy between the subjective experienced level of functioning and he objectively observed level of functioning. Adolescents are frequently reporting an improved ability to concentrate in school or college while at the same time declining in their grades [33].

Even in a population that has a high level of IQ the impairment caused by Marijuana is frequently not accurately perceived. A study with aircraft pilots in a flight simulator showed that the cognitive impairment was accurately perceived during the acute marijuana intoxication, but the impairment was not perceived after 24 h of drug exposure even though the deficits were obviously demonstrated in the simulator [34].

Another study enrolled 112 adolescents in a trial performing neurocognitive batteries also confirmed that marijuana users subjectively reporting "no memory problem" scored lower on average than those users reporting a minor problem and their scores were not significantly different from those reporting a "serious memory problem" [35].

A study including 73 college age daily marijuana users studied them in the context of use but in non-intoxicated stage. The group had above average levels of general intellect. The study participants were tested with a neurocognitive battery utilizing the Finger Tapping Test and the Grooved Pegboard.

The users demonstrated many deficits regarding their memory, problem-solving skills and motivated decision making. Marijuana users appeared less motivated and less persistent in terms of showing effort for completing tasks. Also the Marijuana users showed a greater

loss of consolidation when asked to reproduce learned information [36].

Adolescents are also particularly at risk for the negative effect of marijuana on decision making in their role as beginner drivers on the road and therefore also a danger to others when driving under the influence. Marijuana intoxication leads to impaired driving and increased the risk of collision-related morbidity and mortality by 1.5 to 3-fold [37].

The use of marijuana in adolescents also leads to impairment in attention. A longitudinal study by Tapert et al. has demonstrated this by following adolescent marijuana users over a period of 8 years [38]. Another study by Tait et al., also over an 8 year follow up on adolescents using marijuana confirmed the finding of decreased attention and also showed a decline in verbal memory [39]. Pope and colleagues found that the use of marijuana prior to age 17 was related to poorer performance on verbal memory and fluency tasks as well as verbal IQ [40].

The group of Solowjj et al. demonstrated that the use of marijuana in young adults (on average age 20) led to a delay in recall and showed a decline in learning compared to a non-marijuana using group [41]. The observed impairment was related to the amount of marijuana smoked in this group [41].

It has also been scientifically proven in clinical studies that marijuana-related cognitive deficits include a reduction in the processing speed in addition to the attention impairment. These observations were made in adolescents using marijuana without any psychiatric co-morbidity [42]. The decline in processing speed, reduction in verbal memory, sustained attention and sequencing ability were found even a month after recovery [43].

Structural and neuro-anatomical changes related to marijuana in the brain

Several neuroimaging studies have been conducted to determine the pathophysiology of these disorders in adolescents related to marijuana use.

Marijuana exposure in adolescent years causes changes in the gray as well as the white matter. Marijuana furthermore has been shown to be toxic to the cortical vascular function as well as neurons and microglia.

These morphological changes have been shown in the adult population as well as the adolescents. Some studies have pointed out that female adolescents might be at increased risk to develop marijuana induced structural and neuro-anatomical changes [43,44].

Gray matter

The grey matter is a major component of the central nervous system, consisting of neuronal cell bodies, glial cells, synapses and capillaries. The use of marijuana causes structural changes in the gray matter in various brain regions.

Lopez-Larson et al measured the cortical thickness in marijuana users and compared them to non-users. The group found a decrease in thickness in the right caudal middle frontal, bilateral insula and bilateral superior frontal cortices with increased thickness in lingual, temporal, inferior parietal and paracentral areas in the cannabis users. These findings are linked to the decreased executive functioning [45].

Other studies showed that marijuana use causes structural changes in the hippocampus, which is linked to depression. Other affected areas of the brain by marijuana are the amygdala, a brain region that is central to addictions and affective disorders [46].

A more novel technique is the measurement of the gray matter architecture per gyrification, which is formed by horizontal cortical development and increased tension in the white matter [47].

Another pathological finding was the discovery that the complexity in the prefrontal cortex is reduced, showing a decreased cortical curvature in young adults using marijuana [48].

White matter

The white matter, which is made up of densely-packed bundles of myelinated axons (nerve fibres) and is responsible for efficient connectivity between brain regions. In case of white mater damage, this function is diminished [43] (Table 1).

Depression	Anxiety	Psychosis	ADHD	Cognitive decline
Structural brain damage	COPD	Heart disease	Cancer	Addiction
Fertility	Birth defects	Suicidality	Decline in socio-economic functioning	Immuno-suppression

Table 1: Marijuana is a schedule I substance with an extensive list of toxic effects.

The exposure to marijuana leads to a reduction in the white matter with demyelination as well as axon degeneration and therefore a decrease in slower processing speed, which is particularly harmful in the still developing adolescent brain [43]. Another significant factor in the reduction of cognitive processing are the cannabinoid receptors that are primarily located on neurons but also found on myelinating glial cells [49].

A study from the UK, with a sample size of 99 cannabis users, assessed their brain matter using MRI scans of a specific type known as Diffusion Tensor Imaging (DTI). This advanced technique measures in 3D the rate of diffusion of water molecules through tissues of the body, and allows users to analyze specific tissues and structures with astonishing precision and detail. The group particularly looked at the corpus callosum and found that the mean-diffusivity (MD), which is the main rate that which water molecules diffuse through tissue was significantly elevated, meaning that there is structural damage in the myelin sheath of the neurons [49].

A longitudinal study over a 18 month follow up period demonstrated poorer white matter integrity in the bilateral superior longitudinal fasciculus, bilateral thalamic fibers, right superior temporal gyrus, right inferior longitudinal fasciculus, and left posterior corona radiate [50].

Perfusion/neurotransmitters

The use of marijuana is associated with a reduced cerebral blood flow in the PFC, insular, and temporal regions [51]. Functional neuroimaging studies have demonstrated a lower blood flow in adult users while using or abstinent. The affected brain regions were the prefrontal cortex cerebellum and striatum (Chart 2).

1. Has smoking pot stopped being fun?
2. Do you ever get high alone?
3. Is it hard for you to imagine a life without marijuana?
4. Do you find that your friends are determined by your marijuana use?
5. Do you use marijuana to avoid dealing with your problems?
6. Do you smoke pot to cope with your feelings?
7. Does your marijuana use let you live in a privately defined world?
8. Have you ever failed to keep promises you made about cutting down or controlling your use of marijuana?
9. Has your use of marijuana caused problems with memory, concentration, or motivation?
10. When your stash is nearly empty, do you feel anxious or worried about how to get more?
11. Do you plan your life around your marijuana use?
12. Have friends or relatives ever complained that your using is damaging your relationship with them?

Chart 2: Example for screening questions for marijuana addiction in the adolescent.

Cannabinoid receptors are growing in number in adolescents and are distributed widely throughout the brain. Through the cannabinoid receptors, Marijuana causes changes in inhibitory as well as exitatory neuro-transmitter release. In particular alterations in dopamine, glutamate and GABA release have been shown [52]. Studies utilizing magnetic resonance spectroscopy showed alterations in glutamate, N-acetyl aspartate, creatinine and myo-nositol in the anterior cingulate [53]. Also, myo-inositol/creatine ratios were demonstrated in subcortical area as well as a reduction of myo-inositol in the white matter [52].

Physical toxic effects in the adolescent

Marijuana has systemic toxic effects in the user independently if adolescent or adult. The toxic effects range from increased risk for ischemic incidents due to vasoconstriction and tar deposits to increased risk for COPD or cancers. Those effects may not present in the adolescent right away but manifest later in their life. The use of marijuana negatively affects the fertility due to changes in the hormones FSH and LH. When consumed during pregnancy it puts the fetus at increased risk for birth defects. Pregnancies in teenage years are declining but still a problem in this age group. The impairment in judgment through the marijuana use bears an increased risk for the pregnancy in the teenage-user.

Marijuana is also discussed to have an immunosuppressive effect in the users, especially problematic when consumed in AIDS patients due to the increased incidents of opportunistic infections and therefore mortality.

Conclusion

The use of marijuana in the adolescent population is a severe problem in the current US society and this article is intended to draw more attention to this problem and encourage for further research studies to be conducted. The natural form of cannabis, marijuana, is often times the gateway drug for adolescents and believed to be harmless and non-toxic. Marijuana in its natural form is still not entirely known in its pharmacological ingredients with more than 421 components and more than 60 pharmacologically active cannabinoids.

The current public demand to legalize marijuana in several states for "medical purposes" requires more investigation and research regarding the long term toxic effects of marijuana in adolescents as well as adults for it to be called "SAFE". Further research studies need to be done to analyse the discrepancy of the subjective reported cognitive improvement but worse performance on cognitive tests. Current studies are warning and alerting that the use of marijuana in the adolescent might be related with life-long, permanent cognitive impairment [32].

Looking at the table listing the toxic effects of marijuana, the risks of the use of marijuana outweigh the benefits by far and make the use harmful to the adolescent.

The negative effect of marijuana on the adolescent's mood and thoughts increase the risk of early onset or more severe form of psychiatric conditions: Bipolar disorder, Psychosis, Schizophrenia and even personality disorders.

More attention should be drawn to the screening for substance and in particular marijuana use in the adolescents. The screening should not be limited to the Psychiatrist only. The pediatricians should receive more training to particularly screen their patients for substance use and in particular marijuana use. The assessment of the amount and frequency of marijuana use is important to initiate treatment to reduce the use and to reduce marijuana related harms. Adolescents using marijuana often times have impaired academic performance, poor work performance and low social functioning. Physicians should be able to perform motivational interviewing techniques to counsel the adolescent and refer those to a specialist who are unable to reduce their use or who are experiencing severe toxic consequences from marijuana use.

More studies are needed to show long-term effects of the use of marijuana in the adolescents. Current Studies are often limited in number and follow up period.

References

1. White house office of national drug control policy (2010) Facts and answers to the frequently asked questions about marijuana.
2. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE (2012) Monitoring the future national results on drug use: 2012 Overview, key findings on adolescent drug use. Ann Arbor: Institute of Sociology.
3. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, et al. (1999) Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 2: 861-863.
4. Sautel SS, Sakai JT, Thurstone C, Corley R, Christian Hopfer (2012) Medical marijuana use among adolescents in substance abuse treatment. J Am Acad Child Adolesc Psychiatry 51: 694-702.
5. Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, et al. (2012) Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand 125: 45-53.
6. Grotenhermen F, Müller-Vahl K (2012) The therapeutic potential of cannabis and cannabinoids. Dtsch Arztebl Int 109: 495-501.
7. Harma P, Murthy P, Bharath MMS (2012) Chemisrty, metabolism and toxicology of cannabis: Clinical implicatons. Iran J Psychiatry 7: 149-156.
8. Huestis MA (2007) Human cannabinoid pharmacokinetics. Chem Biodivers 4: 1770-1804.
9. DEA-Drug enforcement agency (2015) The DEA position on marijuana.
10. Crean RD, Crane NA, Mason BJ (2011) An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med 5: 1-8.
11. Degenhardt L, Chiu WT, Sampson N, Kessler RC, Anthony JC, et al. (2008) Toward a global view of alcohol, tobacco, cannabis and cocaine use: Findings from the WHO world mental health surveys. PLoS Med 5: e141.
12. Center for disease control (2014) Smoking and tobacco use.
13. Monitoring the future (2012) NIH, National institution of health.
14. Schneider M, Schomig E, Leweke FM (2008) Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. Addiction Biology 13: 345-357.
15. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, et al. (1999) Brain development during childhood and adolescence: A longitudinal MRI study. Nat Neurosci 2: 861-863.
16. Chadwick B, Miller ML, Hurd YL (2013) Cannabis use during adolescent development: susceptibility to psychiatric illness. Front Psychiatry 129: 1-8.
17. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005) Prevalence, severity\ and comorbidity of 12 month DSM-IV disorders in the national comorbidity survey replications. Arch Gen Psychiatry. 62: 617-27.
18. Fergusson DM, Horwood LJ, Swain-Campbell N (2002) Cannabis use and psychosocial adjustment in adolescence and young adulthood. Addiction 97: 1123-1135.
19. Pedersen W (2008) Does cannabis use lead to depression and suicidal behaviours? A population-based longitudinal study. Acta Psychiatr Scand 118: 395-403.
20. Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, et al. (2012) Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand 125: 45-53.
21. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, et al. (2007) Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. Lancet 370: 319-328.
22. Mathias CW, Blumenthal TD, Dawes MA, Liguori A, Richard DM, et al. (2011) Failure to sustain prepulse inhibition in adolescent marijuana users. Drug Alcohol Depend 116: 110-116.
23. Patton GC, Coffey C, Lynskey MT, Reid S, Hemphill S, et al. (2007) Trajectories of adolescent alcohol and cannabis use into young adulthood. Addiction 102: 607-615.
24. Kandel D (1975) Stages in adolescent involvement in drug use. Science 190: 912-914.
25. Newcomb MD, BEntler PM (1986) Cocaine use among adolescents: Longitudinal associations with social context, psychopathology and use of other substances. Addict Behav 11: 263-273.
26. Nocon A, Wittchen HU, Pfister H, Zimmermann P, Lieb R (2006) Dependence symptoms in young cannabis users? A prospective epidemiological study. J Psychiatr Res 40: 394-403.
27. Lysnkey MT, Health AC, Bucholz KK, Slutske WS, Madden PA, et al. (2003) Escalation of drug use in early-onset cannabis users vs. co-twin controls. JAMA 289: 427-433.
28. Solinas M, Panlilio LV, Goldberg SR (2004) Exposure to delta-9-tetrahydrocannabinol (THC) increases subsequent heroin taking but not heroin's reinforcing efficacy: A self-administration study in rats. Neuropsychopharmacology 29: 1301-1311.
29. Ellgren M, Spano SM, Hurd YL (2007) Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. Neuropsychopharmacology 32: 607-615.
30. Diagnostic and statistical manual of mental disorders (2016).
31. Crean RD, Crane NA, Mason BJ (2011) An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med 5: 1-8.
32. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, et al. (2012) Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci USA 109: E2657-2664.
33. Randolph KR, Turull P, Margolis A, Tau G (2013) Cannabis and cognitive systems in adolescents. Adolescent psychiatry 3: 135-147.
34. Yesavage JA, Leirer VO, Denari M, Hollister LE (1985) Carry-over effects of marijuana intoxication on aircraft pilot performance: A preliminary report. Am J Psychiatry 142: 1325-1329.
35. Lane SD, Cherek DR, Tcheremissine OV, Steinberg JL, Sharon JL (2007) Response perseveration and adaptation in heavy marijuana-smoking adolescents. Addict Behav 32: 977-990.
36. Becker MP, Collins PF, Luciana M (2014) Neurocognition in college-aged daily marijuana users. J Clin Exp Neuropsychol 36: 379-398.
37. Gerberich SG, Sidney S, Braun BL, Tekawa IS, Tolan KK, et al. (2003) Marijuana use and injury events resulting in hospitalization. Ann Epidemiol 13: 230-237.
38. Tapert SF, Brown SA (2000) Substance dependence, family history of alcohol dependence and neuropsychological functioning in adolescence. Addiction 95: 1043-1053.
39. Tait RJ, Mackinnon A, Christensen H (2011) Cannabis use and cognitive function: 8 year trajectory in a young adult cohort. Addiction 106: 2195-2203.
40. Pope HG Jr, Gruber AJ, Hudson JI, Cohane G, Huestis MA, et al. (2003) Early-onset cannabis use and cognitive deficits: What is the nature of the association? Drug Alcohol Depend 69: 303-310.
41. Gonzalez R, Schuster RM, Mermelstein RJ, Vassileva J, Martin EM (2012) Performance of young adults cannabis users on neurocognitive measuresof impulsive behavior and their relationship to symptoms of cannabis use disorders. J Clin Exp Neuropsychol 34: 962-972.
42. Fried PA, Watkinson B, Gray R (2005) Neurocognitive consequences of marihuana-a comparison with pre-drug performance. Neurotoxicol Teratol 27: 231-239.
43. Medina KL, Mc Queeny T, Nagel BJ, Hanson KL, Yang T (2009) Prefrontal morphometry in abstinent adolescent marijuana users: Subtle gender effects. Addict Bio 14: 457-468.
44. McQueeny T, Padula CB, Price J, Medina KL, Logan P, et al. (2011) Gender effects on amygdala morphometry in adolescent marijuana users. Behav Brain Res 224: 128-134.

45. Lopez-Larson MP, Bogorodzki P, Rogowska J, McGlade E, King JB, et al. (2011) Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav Brain Res 220: 164-172.

46. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, et al. (2012) Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. Neuroimage 59: 3845-3851.

47. Joshi M, Cui J, Doolittle K, Joshi S, Van Essen D, et al. (1999) Brain segmentation and the generation of cortical surfaces. Neuroimage 9: 461-476.

48. Mata I, Perez-Iglesias R, Roiz-Santianez R, Tordesillas-Gutierrez D, Pazos A et al. (2010) Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use. Brain Res 1317: 297-304.

49. Rugucci S, Marques TR, Forti MD, Dazzan P (2015) Effect of high-potency cannabis on corpus callosum microstructure. Psychol Med 46: 841-854.

50. Bava S, Frabk LR, Mc Queeny T, Schweinsburg AD, Tapert SF (2009) Altered white matter microstructure in adolescent substance users. Psychi Res 173: 228-235.

51. Jacobus LK, Goldenberg D, Wierenga CE, Tolentino NJ (2012) Altered cerebral blood flow and the neurocognitive correlates in the adolescent cannabis users. Psychopharmaco (Berl) 222: 6756-84.

52. Silveri MM, Jensen JE, Rosso IM, Schneider JT, Yurgelun-Todd DA (2011) Preliminary evidence for white matter metanolite differences in marijuana-dependent young men using 2D J-resolved magnetic resonance spectroscopic imaging at 4 Tesla. Psychia Res 191: 201-211.

53. Prescot AP, Locatelli AE, Renshaw PF, Yurgelun-Todd DA (2011) Neurochemical altercations in adolescent chronic marijuana smokers: 1 proton MRS-study. Neuroimage 57: 69-75.

This article was originally published in a special issue, entitled: **"Marijuana: Clinical, Research, Policy"**, Edited by Norman S Miller