

Study on Toxic Manifestation of Cannabis Sativa: A survey Report

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Abstract

This report is based upon a case study of a 25 years old patient suffering from cannabis use disorder (CUD) in which the addiction intensity and toxicity profile of this drug was investigated. A detailed survey of the intoxication reported in literature and the comorbid conditions were helpful in the treatment plan of this patient such as Alcoholic Anonymous (AA) or Narcotic Anonymous (NA) meetings. The effects were also compared with the commonly used materials of addiction. Based upon its neurotoxicity, an attempt was made to correlate the symptoms of CUD, SARS and Covid-19 with the perspective of effectiveness of Cannabis hypothetically in alleviating the symptoms of Covid-19.

Keywords:

CUD, Marijuana, THC, CBD, Schizophrenia, SARS, COVID-19.

1. INTRODUCTION

1.1. Background of Report:

Case Study:

Harry Jones is a 25 years old male who graduated from Wayne State University with a degree in marketing, works for Mackenzie Corporation and frequently travels for his work. Recently he moved back to his mom's house after breaking up with his girl friend for 5 years, who is also the mother of his 3 year old daughter. He was presented with irritability, insomnia, restlessness, decrease appetite, loss of weight and sometimes anger outburst at his mother.

Mr. Jones is the youngest of three siblings. His father works for Chrysler and his mother is a clerk at the Wayne State administrative offices. His parents got divorced in his sophomore year of high school. He went to Farmington Public School and has a history of smoking weed since high school, perceiving it as harmless and relaxing yet

his desire for it has been increasing. He has been spending significant amount of his time in obtaining, using and recovering from it despite the desire to cut down. Although, Mr. Jones describes himself as a responsible person but lately he talked for his difficulties. His girl friend left him, and his boss gave him a warning for poor performance and not meeting the deadlines. He has been missing the visitation days with his daughter, not hanging out with friends and he has been aggressive towards his parents.

From this description, it was concluded that the patient has Cannabis Use Disorder (CUD).

1.2. Master Treatment Plan:

1.2.1. Problem identified:

Continued Cannabis use causing impairment in daily physical, psychological, relational, and occupational functioning.

1.2.2. Goal:

Withdraw from the use of Cannabis, stabilize physical, psychological, relational, and occupational function.

1.3. Master treatment Protocol:

- i. Discuss the history, quantity, and frequency of cannabis use.
- ii. Schedule Psychiatric evaluation for any possible comorbid condition.
- iii. Monitor compliance with the psychotropic medication if prescribed.
- iv. Schedule physical exam for any coexisting medical condition.
- v. Assess patient's acknowledgement and motivation for change.
- vi. Explore and resolve any ambivalence associated with commitment for change.
- vii. Ask patient to make a list of negative effects

of CUD and positive impact when not using.

viii. Encourage self-efficacy for change.

ix. Offer Motivational Enhancement Therapy and establish rapport.

x. Develop an abstinence contract.

xi. Recommend AA (Alcoholic Anonymous) or NA (Narcotic Anonymous) meetings.

1.4. Introduction of Cannabis Sativa:

Cannabis Sativa is a flowering plant whose phytochemical by-products, hashish and marijuana, are the most widely produced and most frequently used illegitimate drugs in Europe (1. Carla and Marco, 2016). THC, Δ^9 -Tetrahydrocannabinol is the primary psychoactive constituent responsible for euphoria, cognitive effects, and psychotic symptoms in a dose dependent manner as well as the addictive potential of smoked Cannabis (2. Da-Cheng Hao et al., 2015). Material prepared from the flowering tops or leaves is commonly called marijuana and usually contains 0.5–5% THC (3. Daeid, 2005).

Marijuana is consumed in different regions with different names as pot, weed and dagga in various ways such as smoking, vaporizing, and as tea and edibles. Onset of effects is within minutes when smoked and about 30–60 min when cooked and/or eaten (4. Ashton, 2001). Cannabidiol (CBD) is a nonpsychotic derivative of marijuana and attained much attention since it exerts a wide array of therapeutic effects, ranging from anticonvulsive, sedative, hypnotic, antipsychotic, anti-cancer, anti-inflammatory and neuroprotective activities without the mind-altering effects of marijuana or certain pharmaceutical drugs (5. Iffland and Grotenhermen, 2017).

1.5. Etiologic Theories:

Recent legislations had legalized the use of Cannabis in United States and has been more socially accepted and easily accessible. However, the seemingly harmless drug can result into an addiction in some individuals as Cannabis Use Disorder (CUD) with 8.9% probability of the dependence on this substance, A number of studies have been conducted to find the etiology of transition of cannabis use into cannabis use disorder, yet little evidence exists. However, these studies suggest that CUD most likely is a result of a combination of biological and psychosocial factors (Courtney et al; 2017). The most prominent finding of these authors suggested that CUD more likely to develop in males, past substance user, (particularly tobacco), and presence of pre/comorbid psychopathological conditions like mood disorder. Social influences especially peer pressure during adolescence also held significant importance.

The elevated levels of norepinephrine might be due to predisposition or environmental, is an etiological factor in the abuse of wide range of substances, including cannabis (7. Fitzgerald, 2013). Many of the rodent studies supported the hypothesis that acute marijuana / THC administration increases levels of norepinephrine. Neurobehavioural disinhibition (ND) measured in childhood is a leading factor in predicting substance use disorder in young adulthood (8. Feske et al; 2008). The authors also determined the extent of peer pressure which could be held accountable in association of the ND and CUD. Boys (n=208) in the ages of 10-12 years taking maternal and paternal SUD into consideration, paternal SUD, son's ND and son's peer environment predicted

CUD at age 22 with 84% accuracy. It is hard to predict exactly the etiology of CUD but the research has shown that it is related to multiple factors going back to the time of fetal development. The finding focused on the transmissible (intergenerational) and non-transmissible risks which suggested that the paternal substance use disorder predicted infant's temperament that in turn predicted transmissible risk in late childhood presaging CUD. This indicates that it is important to implement prevention before the child consolidates behaviours during middle and late childhood predisposing to cannabis use and cannabis use disorder (9. Tarter et al; 2011).

A family, adoption, and twin study suggested that the use, abuse and dependence of cannabis is heavily hereditary influenced and gene and environment both participate in this disorder (10. Agrawal et al; 2006). However, advanced molecular genetic studies are required to identify the gene contributing the cannabis involvement.

High risk families recruited with fathers with or without substance use disorder and the oldest son in the family of 10, 12, 16, 19 and 22 age groups. The results demonstrated that deviant socializing along with poor parent child relationship were integral causes of cannabis use disorder (11. Tarter and Fishbein, 2011).

The childhood phenotype and environment type were associated with the risk of Cannabis Use Disorder. The participants (n=216 boys) between the ages of 10-12 were evaluated on the basis of self, mothers, and teacher's reports. They were followed up to the ages of 19 and 22 to determine the presence of CUD. Considering the transmissible and non-transmissible liability indices, the results showed that TLI and NTLI both predicted accuracy of 70% and 75%, respectively in CUD by the ages of 19 and 22.

The finding indicated the possibility of screening the SUD and CUD in childhood (12. Kirisci and Tarter, 2009).

1.6. Epidemiology:

Throughout the globe cannabis is still considered as the most used illicit drug, estimated 125-203 million users, with the highest prevalence among the adolescents. Among the adolescents in Europe and North America, 16.4% boys and 12% girls of age 15 reported using cannabis in the past year and 3% boys and 8% girls reported using cannabis regularly (13. Shi and Lenzi, 2015). An increase use of cannabis by adolescents in 38 different countries of Europe and North America after the liberation policies for cannabis revealed that in adolescents, the frequency of cannabis use in their life time abruptly. Among 83,294 boys and 89,600 girls included in the study, 19.85% reported ever use, 15.56% of past year use and 3.32% reported regular use. In general, the boys had higher use than girls.

Due to the new legislation for marijuana people attitude and using patterns has significantly changed (14. Hasin and Shmulewitz, 2020) Among various groups, individual with pain are a new group of people who may be at risk for cannabis use disorder. Marijuana used by individuals with pain and without pain show that cannabis use was more prevalent among the individuals with pain putting them at greater risk for cannabis use disorder. It was suggested that the clinical and public health officials require to look into the prevalence of this group and the healthcare providers should pay special attention to the patients who come for pain management. They also noticed the increase in prevalence of CUD significantly during last decade especially among hospital patients, veteran's health admin-

istration, and patients with pain. Marijuana use amongst adolescents has had its ups and downs. According to a study at University of Michigan and sponsored by the National Institute on Drug Abuse at the National Institute of Health, adolescent marijuana use from 1975 to 2017 peaked in 1979, when 51% of 12th graders reported having tried marijuana before, this was followed by a sharp decline in the 80s, a steady rise back up in the 90s, and another decline in the early 2000s (15. Johnston, et al; 2017). Today, the numbers are slowly rising as many new ways to consume marijuana are available, most notably the ability to vape it. Due to the lack of smell left behind and the easy accessibility of "carts", vaping marijuana can be done quickly and quietly in places such as school bathrooms. The marijuana usage levels amongst high school aged adolescents have been slowly increasing since the start of the decade (Fig-1).



Fig-1: Percentage of high school students who used marijuana during 1975-2017

Perhaps more concerning than the increase in usage, is the high percentage of high school and

adolescents who believed it is not risky to use marijuana regularly, the percentage declined (Figure 2).

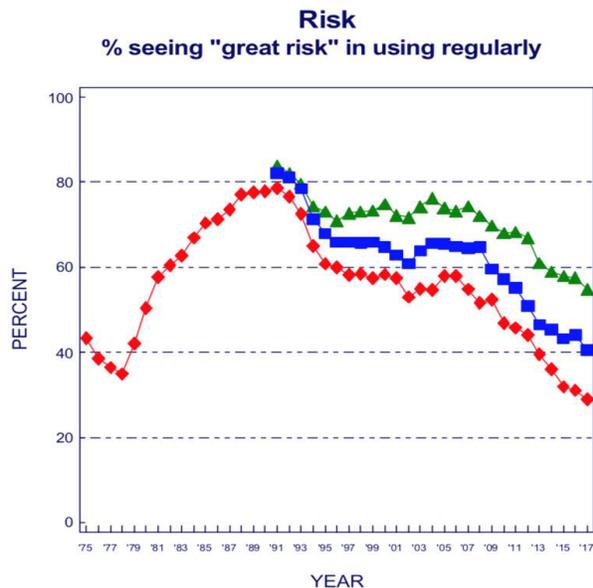


Fig-2: Percentage of high school students who see a risk in using marijuana regularly during 1975-2017.

A study conducted by Hasan and Deborah in 2017 regarding the epidemiology of cannabis and its associated problems in the US, suggested the following:

- i. Time trend in cannabis potency became doubled in seized samples over the last four decades.
- ii. Time trends in prenatal cannabis exposure also increased to 7.5% compared to the past, among pregnant women ages 18 to 25 years.
- iii. Time trends in childhood exposure measured using data from National Poison Data system, indicated that the accidental cannabis exposure to children of 6 years of age had increased from 4.2 million to 10.4 million per year.
- iv. Time trend in cannabis use in adolescents however did not show a significant increase or

decrease compared to previous years.

v. Time trend in cannabis use among adults between 18 to 25 years of age showed increase in overall usage compared to previous years regardless of gender, region, educational level, employment status, however the highest users were males and unemployed (16. Hasan and Deborah, 2017).

1.7. Comorbid Conditions:

A group of researchers explored that the most common comorbid condition associated with all substance abuse is schizophrenia. Other than the two legal substances, alcohol and tobacco, cannabis is the most common drug used by schizophrenic patients. A study was done on a specific population of substance abusers and the results showed that as compared to general population, substance use disorder was 4.6 time higher in this population. Substance abuse especially cannabis was considered as an important risk factor for developing schizophrenia. On the other hand, it has also been concluded that substance abuse may be the contributing factor in an early onset of schizophrenia and the patients who are consistent with substance abuse are more likely to have more frequent and longer duration of hospitalization. There is still a need to do more research on the effects of cannabis on the morphology of the brain, however it is evident that cannabis abuse negatively effects the patients of schizophrenia in many ways including cerebral volume loss (17-18. Malchow et al; 2012, 2013). In another study done on the relationship of cannabis and development of schizophrenia, the authors studied that cannabis plays its role on the

onset of schizophrenia spectrum. This study was done in five different countries and the results clearly showed that the consistent use of cannabis does increase the risk of schizophrenia and other psychotic disorders (19. Smit et al; 2004). The authors concluded following six noteworthy findings through their studies:

1. The use of cannabis can double the risk of schizophrenia.
2. Youth are more to expose themselves to the risk compare to other population.
3. Increase in the usage increases the risk.
4. People who are vulnerable are also at high risk.
5. The vulnerability covers a broad spectrum and not easy to characterize.
6. Although the risk may appear small in numbers but can be lethal in clinical terms.

Presently many researches are dedicated to study the relationship of cannabis involvement and other psychiatric disorders. In a study conducted on family, adoption, and twin, the two psychiatric disorders that stand out in particular were major depressive disorder and conduct disorder. Findings suggested that genetic influences and common vulnerability both could be a cause of deviant behaviour (Agarwal, et al, 2006).

In an another investigation, it was explored the emergence and discovery of endocannabinoid system has augmented the study of co-relation between cannabinoids and psychotic disorders like schizophrenia, bipolar disorder, major depressive disorder and anxiety disorder has become easier (20. Leweke and Koethe, 2008).

Based upon the previous research along with the recent replication studies suggested that consistent use of cannabis doubles the risk for psychotic symptoms and schizophrenia.

Another study was conducted on marijuana use amongst drivers during 2013 and 2014, and of the 11,100 drivers surveyed in 24 different states, 718 were between 16-19 years of age.

The survey also collected other data such as the household income of the drivers, how often the drivers use tobacco, how often the drivers drink alcohol, the level of education completed by the drivers, and the employment status of the drivers (21. Pressley et al., 2019). Drivers who weren't legal adults were given oral tests only while drivers who were 18 and older were given both oral and blood tests. A positive test was defined as either testing positive on the blood test or oral test, a negative test was defined as being negative on both. A positive THC test was defined by a minimum concentration of active THC metabolites in 1ng/mL and 2ng/mL in blood and in oral tests respectively. Of the 718 teenaged drivers, 203 (28%) were either tested positive for THC or admitted to smoking marijuana in the past years.

The authors presented the data in Fig. 3 showing how often teenagers smoked marijuana impacted how often they were likely to smoke tobacco, as the numbers rose higher for both marijuana and tobacco based on how often the drivers surveyed smoked marijuana.

They also investigated that how alcohol use contributed to a positive THC test. The study found that drivers who began drinking alcohol before becoming a legal adult were over twice as likely to test positive for THC (Fig. 4).

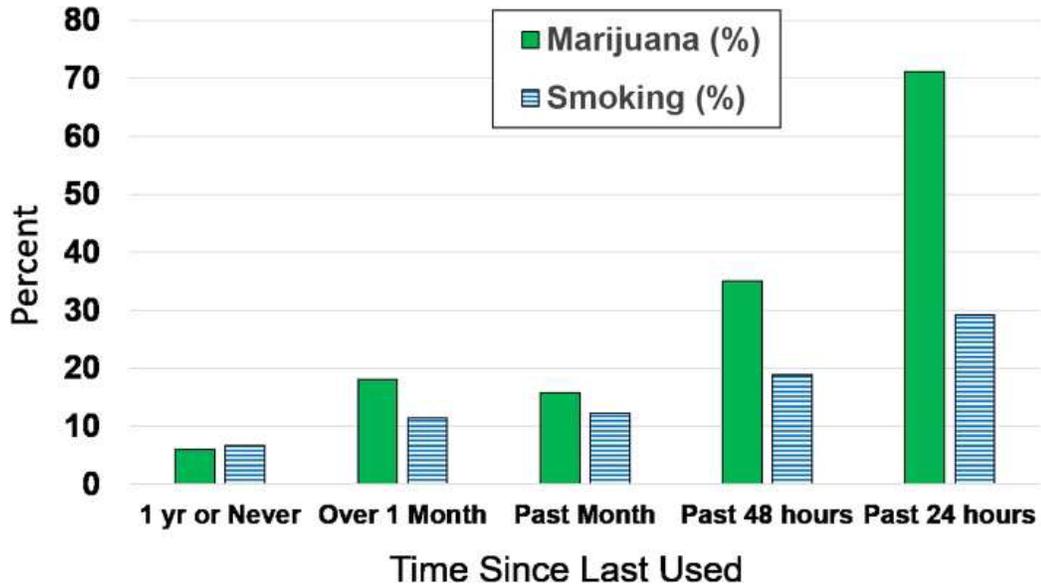


Fig-3: Correlation between Marijuana use and Tobacco use

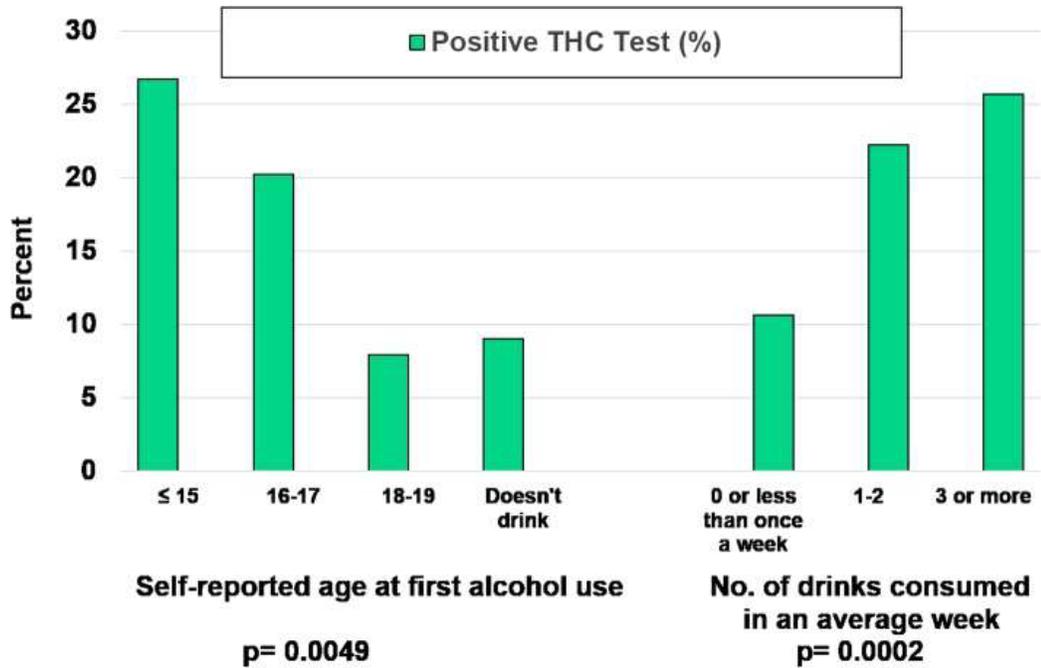


Fig-4: Correlation between Alcohol use and Marijuana use

With over a quarter of teen drivers testing positive for THC use, and the study showing that students who tested positive are more likely to be using other substances. From these findings, it is clear that this issue needs to be taken more seriously.

2. MATERIAL AND METHOD

Based upon the method of Walker et al; 2011, a trial done earlier was the random selection of students into two different types of treatment for marijuana use required as baseline meetings such as Motivational Enhancement Therapy (MET) and Educational Feedback Control (EFC). In MET sessions, counselors encourage students

to reach their own conclusions and guide them by asking about how they started marijuana use, their concerns about their use, and how they see their use progressing both in the near future and in the long-term. In EFC sessions, students watched presentations about cannabis use and counselors were told to avoid using MET tactics all together. Out of 205 teenaged participants, 103 were put into MET, and 102 into EFC.

3. RESULTS AND DISCUSSION:

The results given in Table 1 showed that both methods decreased marijuana use in the teenagers.

Table 1: Cannabis Use and Related Problems during 360 Days (12 months) study

Assessment						
Treatment Conditions	Base Line		3 months		12 months	
	M	SD	M	SD	M	SD
MET EFC	Days of Cannabis Use					
	40.23*	14.28	31.80*	19.67	33.71*	22.27
	37.69*	16.06	34.53* ^b	19.78	34.24*	34.24
MET EFC	Number of Dependence Symptoms					
	3-37*	2.07	2.70*	2.01	2.74*	1.99
	3.45*	2.09	3.02*	2.00	2.92*	2.11
MET EFC	Number of Abuse Symptoms					
	1.38*	1.16	1.05*	1.04	1.10*	0.95
	1.59*	1.11	1.30**	1.04	1.14*	1.03
MET EFC	Number of Cannabis Problems					
	18.47*	13.47	14.68*	10.39	13.08*	10.35
	19.13*	12.31	14.24*	10.18	14.14*	10.32

Note: * = Significant data, p<0.05 , ** = Highly significant data, p< 0-01 ? statement needs verification.

M = Mean of 103 MET and 102 EFC, SD = Standard Deviation, MET = Motivational Enhancement Therapy, EFC = Educational Feed Back Control

Changes in marijuana usage over time for high school students were put through different therapy models (12 Walker et al., 2011).

According to one study, 153 adolescents were randomized to three types of interventions, a. Motivational Enhancement Therapy and Cognitive Behaviour Therapy. b. Motivational Enhancement Therapy, Cognitive Behavioral Therapy (CBT) along with abstinence based contingency management, and c. Cognitive Motivational Enhancement Therapy, Cognitive Behaviour Therapy, Contingency Management Therapy in addition to parent training. The findings suggested that overall youth receiving clinical and home-based contingency management along with MET and CBT increased rates of abstinence compared to the other two (23. Stranger and Ryan, 2015).

3.1. Future Research in perspective of COVID treatment and prevention:

Apart from the toxic manifestation of cannabis sativa, it is revealed from the literature that cannabinoids are also found effective in the treatment of many health conditions such as neuropathic pain, spasms and movement disorders (24. Grotenhermen & Muller-Vahl, 2016. 25. Kristen Muller-Vahl, 2015). Keeping in view the promising health effects of Cannabinoid, researchers are investigating its effectiveness against COVID-19 Corona Virus. Most recently a research letter is submitted based upon the hypothesis that cannabidiol (CBD), being non-psychoactive exerts a wide range of immune-modulatory and anti inflamm-

atory effects (26. Giuseppe et al., 2020).

According to them, CBD might be effectively used as a candidate drug against COVID-19 pandemic due to its two possible effects:

a) Decreasing the uncontrolled cytokine production, the progression of pulmonary fibrosis is inhibited, hence improving lung function in recovered patients (27. Pedersen, 2020).

b) Ability to down regulate angiotensin-converting enzyme 2 (ACE2) and transmembrane Serine Protease 2 (TMPRSS2) receptors which are essential viral gateways in oral, lung and intestinal epithelia constituting important routes of SARS-COVID-19 invasion (28. Wang et al., 2020). This effect not only blocks the entry into susceptible hosts but it also reduces the bioavailability of ACE2 receptors in infected tissues, thus limiting the progression of the disease. Based upon the hypothesis, much work is crucial to explore CBD therapeutic potential in COVID-19 patients and its effectiveness in recovered patients.

4. CONCLUSION

The finding of much research suggests that the cannabis use disorder is more common in adolescents and in adulthood. Therefore further research on the adolescent brain cognitive development might unveil the etiology of this disorder and can be applied as preventive measure. It would be beneficial for research on cannabis use disorder in biomedical research and the effects of cannabinoids on the neurotransmitter which

will open avenue for effective intervention.

Hypothetically, cannabidiol is claimed to be effective in alleviating some symptoms of SARS-COVID (Severe Acute Respiratory Syndroms-Corona Virus) which needs more research to explore its potential.

5. REFERENCES:

1. Carla Cannizzaro, Marco Diana (2016). In: A Neuropathology of Drug Addictions and substances Misuse. Second Edition.
2. Da-Cheng Hao Xiao Jie Gu Pei Gen Xiao(2015) Medicinal Plants 1st Edition chapter 11; Chem, Biology and Omics. Hardcover ISBN: 9780081000854. eBook., ISBN: 9780081001035. Wood head Publishing.
3. Daeid, N.N. (2005). In: Encyclopedia of Analytical Science (Second Edition).
4. Ashton CH (2001). "Pharmacology and effects of cannabis: a brief review". Br J. Psychiatry.178: 101–106.
5. Iffland K., Grotenhermen F (2017). "An Update on Safety and Side Effects of Cannabidiol": The Review of Clinical Data and Relevant Animal studies. Cannabis Cannabinoid Res.s. 2017; 2:139–154. doi: 10.1089can.2016.0034.
6. Courtney, K.E, Mejia, M.H, Jacobus, J.2017 " Longitudinal Studies on the Etiology of cannabis Use Disorder: A Review". Current Addiction of Report Volume 4, 43-52.
7. Paul J Fitzgerald (2013). "Elevated Norepinephrin May Be a Unifying Etiological Factor in the Abuse of a Broad Range of substance: Alcohol, Nicotine, Marijuana, Heroin, Cocain and Caffein Substance Abuse: Research and Treatment: 171-183.
8. Feske, U; Ralph E. Tarter,L Kirisci, Zhongcui Gao, Maureen Reynolds & Michael Vanyukov in (2008). "Peer Environment Mediates Parental history and Individual Risk in Etiology of Cannabis Use Disorder in Boys: A 10 Year Prospectives Study, The American Jr of drug and alcohol abuse". 307-320.
9. Tarter RE, Kirisci L, Mezzich A, Patton D.K (2011). "Multivariate Comparison of Male & Female Adolescent Substance Abusers within accompanying Legal Problem" J Crim Justice 39(3):207–211.
10. Agrawal, Arpana, and Michael T Lynskey L 2006. (2006). "The Genetic Epidemiology of Cannabis abis Use, Abuse and Dependence", Addiction 101. 6: 801–812.
11. Tarter, Fishbein(2011). "Deviant Socialization Mediates Transmissible and Contextual Risk on Cannabis Use Disorder Development: The Prospective Study." Addiction (Abingdon, England) 106.7: 1301–1308.
12. Kirisci, Tarter (2009). "Prediction of Cannabis in Use Disorder Between Boyhood and the Young Adulthood: Clarifying the Phenotype and Environment." The American journal on an addictions 18.1:36–47.
13. Shi, Lenzi (2015). "Cannabis Liberalization & Adolescent Cannabis Use: A Cross National Study in 38 Countries." PloS one 10.11: e0143 562-e0143562.
14. Hasin, Shmulewitz (2020). "U.S. Adult with Pain a Group Increasingly Vulnerables to Non medical Cannabis Use and Cannabis L Use Disorder 2001-2002 and 2012–2013."L. The American journal of psychiatry, 177.7:661-618.Web.
15. Johnston, L., Meich, R., O'Malley, M., Bachman, J., Schulenberg, J., & Patrick, M. (2017). "Key Findings on Adolescent Drug Use" <https://www.monitoringthefuture.org/pubs/monograph/mtf-overview.pdf>.
16. Hasan, Deborah (2017)". US Epidemiology of the Cannabis Use and Associated Problems." *Neuropsychopharmacology* (New York, N.Y.) 43.1 : 195-212.
17. Malchow, B., Hasan, A., Fusar-poli, P., Sc, T Schmitt, A., Falkai, P., & Wobrock, T.(2013) "Cannabis abuse and brain morphology in schizophrenia: A review of the available evidence". *The European Archives of psychiatry and Clinical Neuroscience*, 263(1), 3-13.
18. Malchow, Berend (2012). "Cannabis Abuse and Brain Morphology in Schizophrenia: The Review of the Available Evidence." *European archives of psychiatry and clinical neurosci*, 263(1), 3–13.

19. Smit, Filip, Linda Bolier, and SJ Pim Cuijpers in (2004) "Cannabis Use and the Risk of Later of Schizophrenia: A Review." *Addiction* (Abingdon, England) 99.4: 425–430.
20. Leweke, F. Markus, and Dagmar Koethe 2008. "Cannabis and Psychiatric Disorders: It is not only Addiction." *Addiction biology*, 13.2:264-275.
21. Pressley, J. C., Arora, A., & Sarmah, R. 2019. "Marijuana use in U.S. teen drivers: a comparison of a road-side survey of reported use & fluid test for tetrahydrocannabinol 5 (THC)". *Injury epidemiology*, (Suppl 1), 25, <https://doi.org/10.1186/s40621-019-0204-0>.
22. Franjo Grotenhermen & Muller-Vahl (2016). RP "Medicinal Uses of Marijuana and cannabinoids". *Critical Reviews in Plant Sciences*. Vol. 35 issue 5-6: Cannabis. Published online: 17 Feb 2020.
23. Kirsten R. Muller-Vahl, In: *Cannabinoids in Neurologic and Mental Disease*, 2015. Edited by Liana Fattori. DOI: <http://doi.org/10.1016/C20130-00592-0>.
24. Giuseppe Esposito, Marcella Pesce, Luisa Se guella, Walter Sanseverino, Jie Lu, Chiara Corpetti, and Giovanni Sarnelli. (2020). "The potential of cannabidiol in the COVID-19 pandemic: hypothesis letter". 8 May 2020:CC BY 4.0- <https://doi.org/10.22541/au.1588994349.98427987>.