TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 6
Number 2 *Spring 2013*

1-1-2013

Can Marijuana Be Harmful When Used Prenatally or During Adolescence?

Penninah Dean
Touro College

CAN MARIJUANA BE HARMFUL WHEN USED PRENATALLY OR DURING ADOLESCENCE?

Penninah Dean

Abstract

Marijuana is a popular recreational drug with a strong following campaigning to legalize it for both medicinal and recreational use. This paper serves to illustrate the harmful effects of marijuana use as it pertains to prenatal, adolescent and adult use. By understanding the methods of absorption and mechanism of interaction in the body, we can see a correlation between the effects of marijuana and its toxicity. Through extensive research of case studies on marijuana use we were able to determine marijuana's harmful effects physically, developmentally and cognitively. Through these methods of research, it can be concluded that marijuana has detrimental effects on the developing body in utero ,as well as, during adolescence. Furthermore, marijuana has consistently been found to cause long term damage such as short stature, attention span, and verbal retention (Solowij, et. al. 2011). In adults, smoke inhalation of the substance has been found to be more detrimental than the smoke inhalation of tobacco. While marijuana touts a variety of medicinal benefits in its application as a form of palliative care, its toxicity and the prolonged adverse effects of the substance are too strong to ignore.

Introduction:

Cannabis is one of the first plants to have been used medically, recreationally, and spiritually dating back 5000 years, with the first documented medical use in Central Asia and later in China and India (Pertwee, 2006). Cannabis is the most widely used illicit recreational drug after the three most popular substances, tobacco, alcohol, and caffeine (Green, 1998). Since its discovery, cannabis has been used by millions to both induce pleasure and alleviate pain. Physicians have prescribed it for a plethora of ailments until the government classified it as a Schedule I substance, rendering it illegal, and without medical value.

There is a lot of effort being done by the public to try to legalize marijuana with claims that there is no basis for the fear and anxiety the public is placing on the drug, and it is in fact a benign substance. (NORML, 2013). There are surprisingly limited resources for research done on marijuana, largely due to the fact that it is difficult to find subjects willing to cooperate with a study concerning their illegal behavior. With over 300 million users worldwide, 28 million of which live in the United States, it is important to educate the public about the substance, how to use it safely, and if it exhibits adverse effects (Diaz, 1997).

The purpose of the research done in this paper is to ascertain the safety or dangers of marijuana, focusing on a few aspects to determine if it is in fact harmless. It concentrates on the repercussions of prenatal use and its effect on the fetus,its effect on adolescents and determining if there is any observable long term damage.

Method Used:

The author's research was done using Touro College's search engines such as ProQuest,

Penninah Dean graduated in June of 2013 with a B.S. in Biology. She is currently a Nephrology Research Assistant at Evanston Medical Center.

MEDLINE, and EBSCO, as well as research articles found through PubMed and Google Scholar. The method of research included reviewing studies and published articles that have been peer reviewed. In certain cases the author questioned the validity and accuracy of the methods used to attain the data presented and documented their uncertainty of the method of research. In other cases the author presented conflicting arguments to refute some peer reviewed studies to present that not all studies can be accepted at face value.

Marijuana Intake and Potency:

Cannabis, colloquially known as marijuana, is a recreational drug whose leaves, flowers, and stems are all utilized in its use. The chemical compounds found within the Marijuana plant identify it as a member of the cannabinoid class. The cannabinoid plant, whose scientific name is *Cannabis sativa,* has a distinctive smell that is similar to that of skunk musk. The described effects of marijuana are relaxing, calming, mellowing, and sometimes anxiety and paranoia provoking. Collectively, these effects are referred to as a 'high.' (Sharman, et. al. 2013).

The predominant psychoactive component in marijuana that determines its potency is delta-9-tetrahydrocannabinol, or THC, and was only isolated in 1964. This molecule is the chemical stimulant in the Cannabis plant that produces the altered states of consciousness in the user.

THC actually exists as Tetrahydrocannabinolic acid, THCA, in the Cannabis plant and is the biosynthetic precursor of THC. Conversion of THCA to THC occurs through burning of the plant. Combustion causes decarboxylation to occur on the THCA converting it to the more psychoactive THC molecule (Hazekamp, et. al. 2005). The depth or strength of the psychoactive component of the cannabis is highly dependent upon the growing conditions and the genetic strain of the plants (Copeland, et. al. 2006).

There are a variety of common methods for marijuana intake. These include but are not limited to smoking the dried leaf of the plant in a the form of a rolled cigarette or "joint", using a water pipe or "bong" to inhale the fumes, consumption in food, inhalation of vapors through a vaporizer, and ingestion of the plants oils. Smoking is the most common and preferred route of intake but it is dulled by the fact that only 5-14% of the smoke is actually THC, and 30-80% of the smoke in the "joint" is lost to escaped smoke (Copeland, et. al. 2006).

Smoking in itself is a dangerous method of intake as it is harmful to the lungs and respiratory system. Marijuana smokers are subject to the same dangers and health risks as tobacco smokers with similar negative results such as respiratory distress, asthma, cardiovascular disease, lung and esophageal cancers (Ellenhorn, Barceloux, 1988).

The second method of choice involves using a water pipe commonly known as a "bong". The bong minimizes the THC lost in the smoke because it is all contained within the bowl and then effectively inhaled. This method can be dangerous due to the larger amounts of carbon monoxide and tar inhaled. Smoking hashish, which is the resin from the plant smoked in a pipe, is less common but is done by adding a few drops of oil to tobacco or cannabis leaves and smoking it in a joint. Another alternative is heating the oils and inhaling the vapors. The oil can also be incorporated in food and consumed, but produces less of an intense high and causes a delayed onset of effects (Copeland, et. al.

2006).

Newer methods, such as the use of vaporizers, have been utilized and have less harmful effects. These machines heat the cannabis and trap the tar and toxins in a special chamber allowing only the THC to be inhaled without the added harmful smoke. This is a useful method for patients who are using marijuana to aid in palliative care and treat illnesses. Through this method they are able to maximize the benefits of marijuana use without risking further damage to their health. Inhalers are also available for oral doses of THC, once again created for the purpose of medical palliative care (Martin, Wiley, 2004).

Chemical Pathways of THC:

THC is an extremely potent chemical and takes only a matter of seconds to enter your bloodstream and reach your brain. When smoked, it takes effect almost immediately and can last anywhere from 1-3 hours. When consumed in food there is a delayed onset of the desired effect, but the THC stays in your system for a longer period of time. Though the full mechanisms of THC still remain unknown, neuroscientists have some information about its effects on the brain (Diaz, 1997).

To understand how THC is interacts with the brain's cells, we must first understand the mechanisms that the brain uses to communicate. Neurons are the cells of the brain that transmit information. Neurons interact with each other through a chemical messenger system known as neurotransmitters. Neurotransmitters attach to protein structures imbedded in the membrane of the receiving neuron known as receptors. The attachment of neurotransmitters to these receptors facilitates the transmission of important information from one cell to the other. Each neuron has thousands of receptors and each receptor is specific to a certain neurotransmitter (Diaz, 1997).

THC is a cannabinoid and is therefore able to mimic endogenous cannabinoid neurotransmitters, such as N-arachidonoylethanolamine (anandamide) or 2-arachidonoyl glycerol. The discovery of these endocannabinoids in 1992 by Israeli scientist Raphael Mechoulam emerged from a study in which he was trying to determine the purpose of cannabinoid receptors in the body (Devane, et. al. 1992). It was discovered that these endocannabinoid neurotransmitters are released by the body into the brain when the body senses an elevation in intracellular calcium. The THC binds to the cannabinoid receptors in place of the anandamide and therefore activates the appropriate neurons that would alternately be activated by anandamide (Sharman, et. al. 2013). THC exerts a majority of its influence through the midbrain reward center, triggering dopamine release in the prefrontal cortex which causes marijuana to have an addictive quality (Kogan, Mechoulam, 2007).

The presence of THC in the brain interferes with the neurons' normal function by artificially stimulating the cannabinoid receptors. Certain portions of the brain have concentrated cannabinoid receptors while others contain only a small number. These receptors can be found in areas of the brain including; the cerebellum, hippocampus and basal ganglia, areas that influence pleasure, memory, concentration, sensory and time perception, as well as coordinated movement. Therefore, THC can affect the sensations associated with thefunctions of these regions of the brain in which the cannabinoid receptors are found, resulting in the sensation of being 'high' (Devane, et. al. 1992).

The largest portion of the cannabinoid receptors are found in the hippocampus which is located in the medial temporal lobe, beneath the cortical surface of the brain and is associated with short term

memory. THC therefore, has the greatest effect on that portion of the brain, explaining why users typically report having trouble with short term memory. The cerebellum and basal ganglia have many cannabinoid receptors as well and therefore those under the influence of THC also report problems with coordination and muscle movements (Sharman, et. al. 2013).

There are two types of cannabinoid receptors identified as CB1 and CB2, in order of their discovery. These receptors act through inhibiting adenylate cyclase. The CB1 receptors are primarily found in the central nervous system, brain and nerve tissue, specifically the basal ganglia, hippocampus, cerebellum, and cerebral cortex, as well as, on the peripheral neurons. Their main function is to mediate inhibition of on-going release of certain excitatory and inhibitory neurotransmitters. CB2 is found in non neuronal cells in immune system tissues such as leukocytes, the spleen, and bone marrow, and was first discovered in human leukemia (Green, 1998).

Marijuana Toxicity:

An important factor to consider is the toxicity level of marijuana. In comparison with regular tobacco smokers, marijuana smoke creates a greater cardiovascular burden due to the high levels of carbon monoxide and tar found in cannabis resulting in a heavy respiratory burden on the smoker.

Marijuana smokers are also known to take larger, deeper puffs and hold the smoke in their lungs for a longer period of time. Because of this practice, the retention of tar in the respiratory tract is one third greater than the amount of tar built up from tobacco smoke. Additionally, smoking marijuana results in much higher level of carboxyhemoglobin than its counterpart, tobacco. Regardless of the THC content, the smoking of cannabis in itself yields a higher carbon monoxide and tar weight on the respiratory tract (Wu, et. al. 1988).

Marijuana has also been found to exacerbate psychotic illnesses in susceptible users, particularly schizophrenia. After testing the correlation between THC and psychosis, marijuana was found to cause consequent anxiety and neuropsychological impairment in users. THC can induce a transient, acute psychotic reactions in psychiatrically well individuals (Rais, et. al. 2008; Barch, Smith, 2008).

Minutes after a dose of THC is delivered in an individual there are notable deficits in working memory and executive functions with a trend towards an impaired episodic memory. This is significant as it is well established that schizophrenia is associated with deficits in those functions (Rais, et. al. 2008; Barch, Smith, 2008). Although the data is telling, the properties of THC are highly dose dependent with a possibility for bidirectional effects. There is also not much explanation of why some individuals are more susceptible to psychotic symptoms than others.

Marijuana is absorbed in the bloodstream from the lungs within minutes of inhalation generating an extremely immediate reaction in the body with the swift onset of a ‘high.’ The degree of intensity of the high depends on the quality of the cannabis, the method of use, and the experience of the user. Familiarity is a factor because a more experienced user will know how to maximize the inhalation, but also may be immune and therefore unaffected by some of the THC absorbed (Copeland, et. al. 2006). Immunity occurs when the body is chemically altered and builds a certain level of tolerance to the presence of marijuana thus requiring a higher dose to attain identical results from the previous use. The effects of tolerance can be dangerous when the subjects gradually increase their dose to achieve a certain

degree of high, while compromising his body and health. While the THC carries out it psychoactive effects, it is simultaneously harming the body's cardiovascular system by lowering blood pressure and increasing heart rate: a potential danger for chronic marijuana users (Gorelick, et. al. 2013).

Marijuana and Fetal Development:

To further understand the toxicity level and dangers of the substance, we must observe its effects on a developing fetus. Studies have been conducted that test the neurodegenerative effect of cannabis exposure on a developing rodent's brain. Tests like these help scientists build a parallel analysis on the effects of cannabis in human neonatal development.

Because of the differences in human and rodent development, analyses were done on a seven day old rodent which is most similar to a third trimester fetus. Perhaps the most obvious limitations to this study is that testing was done exclusively on rats rather than relying on information gathered from actual human case studies and assessing the available neurodegenerative data. Furthermore, the fact that the rodent was not in utero during testing raises questions as to the environmental differences in the conditions of the third trimester of a human fetus. One might argue that there is a level of neonatal protection when a child is in the womb, and that could protect it from foreign toxins as opposed to a rodent pup that has to fend for itself. There can also be claims that a child in utero may be exposed to *more* toxins due to the direct stream of oxygen and nutrition passed from the mother, therefore exposing the fetus to greater risk when its body is still vulnerable and reliant on maternal nutrients rather than depending on its own immune response.

There is evidence, however, supporting the research done on rodents by studying the effects of marijuana on a fetus during the second trimester. Smoking of marijuana was found to have a significant effect on the stature of the unborn child. There is an additional increased risk of premature birth, stunted growth, and morbidity if the offspring is that of an adolescent even if their levels of drug use are lower than those of adult pregnant women (Cornelius, et. al. 2002).

Further evidence can be found in preschool children who were assessed for sustained attention after fetal exposure to marijuana. In these studies, children were found to have various levels of decreased sustained attention. Although this implies that marijuana can have an adverse direct effect on the fetus, the fact that these mothers were users of other drugs including alcohol and tobacco, complicates analysis. Therefore, although there is conclusive data linking marijuana to these results, it is difficult to isolate which substance was the precise cause of the inattentiveness (Fried, et. al. 1992).

With an increase of admitted dose of marijuana use, however, there was a correlated increase in the failure of the exposed children to maintain vigilance and sustain information appropriate to their grade level. There is also a greater likelihood of omission errors, indicating a lack of attention and a described impulsivity and hyperactivity that grew with increasing prenatal dose exposure (Noland, et. al. 2005). These effects were predominantly exhibited in preschool aged children as altered inattentive behavior and if exposed to these drugs at a young age, they also exhibit greater trouble with behavior and focusing,

Double blinded studies such as these are well assessed and dependable due to the fact that the testers are not aware of the substance exposure status of the children and therefore minimizing biased

answers or observations. There are limitations as noted previously as many of the mothers of the children tested were exposed to various drugs as well. This limits the scope of observation and obscures our view as to which of the substances were the cause of the inattentiveness. (Richardson, et. al. 2002).

Experiments on pregnant mammals have shown adverse effects and though the results have been quite supportive of the data, it remains difficult to predict how similar levels of THC would affect pregnant humans. One aspect that has been neglected by these studies is the adverse effect that smoke inhalation may have on the child. Although THC in itself is proven to be detrimental to the fetus, there is an added risk when marijuana is smoked, which is usually the case since that is the most common form of intake. Although there are some human studies revealing the effects on a fetus, there is limited data available due to the shortage of people willing to be included in a study (Jutras-Aswad, et. al. 2009).

Clearly, marijuana use and exposure during pregnancy is extremely harmful to the unborn child. THC is especially dangerous due to the ease in which it is able to cross the placental barrier, therefore entering the fetus's blood supply where it could cause adverse effects. The THC builds up in the fat and liver tissue of the mother and is then passed through the placental barrier. The levels of THC present can be easily measured in the amniotic fluid, with stronger concentrations yielding more harmful results. The speed of transfer is essential because it enables the drug to achieve its pharmacological effects once it comes in contact with the fetus. Consequently, injection of THC during early pregnancy in rodents produced a seventy percent feticide (Harbison, Mantilla-Plata, 1972).

Additionally, negative effects of the marijuana are also observed if the fetus survives. Once the child develops, they can exhibit; an altered response to visual stimuli, increased tremulousness, problems with sustained attention and memory, and poor problem-solving skills (Diaz, 1997).

Adolescent Use:

The number of teenagers informed of the harmful effects of marijuana is decreasing, and consequently there is an increase in adolescent daily marijuana smokers. Marijuana can have an effect on the brain for users who began to smoke during adolescence, as opposed to adulthood. This creates a noticeable decline in IQ from the point of adolescence to adulthood. Through standardized IQ testing it was determined that there was an average of an eight point decline of IQ by mid age. There is a significant impairment of cognitive function, specifically related to attention and memory, and there is an increasing vulnerability to psychosis. There is no proof that stopping use of marijuana will improve cognitive function, and the effects of persistent cannabis remain, causing a neuropsychological decline. Many teenagers and even clinicians are not aware of the high probability of intellectual or psychopathological impairment due to the neurotoxic effects of THC (Meier, et. al. 2012).

Long term cannabis use is specifically detrimental to the white matter of the brain in adolescence and early adulthood. Magnetic Resonance Imaging devices make it easy to determine the portion of an individual's white matter that has been affected. Heavy cannabis use affects axonal connectivity and impairs fimbria of the hippocampus. This is due to the many cannabinoid receptors present in the developing white matter of the brain in fibre pathways (Zalesky, et. al. 2012). The age of commencement of use of cannabis is crucial in determining its effect on white matter, the earlier the onset of use, the more detrimental its effects. This is also in line with extensive research that establishes

a link between long term marijuana use and the onset of schizophrenia as discussed previously (Rais, et. al. 2008).

Overall, cannabis use is more detrimental to the cognitive effects of a growing adolescent than in adults. Unfortunately, marijuana has always been linked to younger users, where it has the greater effect on the subject's cognitive function. Even more so, smaller doses of marijuana pose a greater risk to the developing brain than larger doses will have on a fully developed adult brain. (Solowij, et. al. 2011)

Tested at differing intervals of exposure; before use, during, and after, cannabis users are found to be more anxious, more susceptible to depression, and have lower cognitive abilities than their counterparts. Those that used marijuana consistently have lower verbal learning and memory scores than even alcohol users and control groups alike. There is also impaired retention, storage, and retrieval in cannabis users. Cannabis at low doses in adolescents is still proven to be destructive. The earlier the use of cannabis, and the more frequent, the greater the damage associated with the brain even once cannabis use has ceased (Solowij, et. al. 2011). A convincing amount of data builds a strong correlation between the use of marijuana and impaired cognition. This demonstrates that even in low doses, cannabis can impair the memory of young adults (Reynolds, Parfit, 1993).

Debate:

In a 1992 study, information was published concerning marijuana safety. The scientists, Nahas and Latour, (1992) concluded that extended marijuana use caused prolonged impairment of psychomotor performance; impairment of memory in adolescents; cancer of mouth and jaw; fetotoxicity; an increase in the incidence of schizophrenia; and leukemia in children of marijuana smoking mothers.

Soon after reviewing the information presented, further research was conducted to determine its accuracy. Regrettably, the additional investigation into the study confirmed that eighty percent of the citations were inaccurate and numerous others were misrepresented or biasedly reported. Hence, it is certainly necessary to inquire further whenever new research material is presented, and to be aware of possible discrepancies in any form of research (Macdonald, Gregory, 1994). This of course does not discredit all the research presented, but advises the reader to always verify sources and inquire further.

Another instance of contradictory studies is a 2003 analysis stating that cannabis use was found to cause impairment in both cognitive function and mood (Klugman, Gruzelier, 2003). A later review in 2006, however, noted that workers reported that they performed equally well in controls, working memory, and selective attention tasks as their counterparts (Wadsworth, et. al. 2006).

In addition to possible discrepancies with research studies, there are other possible perspectives on marijuana. While the effects of smoking marijuana itself can be harmful to the health of an individual, and by all accounts it is extremely toxic in young adults as well as fetuses, it is not considered a highly toxic substance. Marijuana is unique in that it has an extremely high lethal dose. Meaning, an individual would have to consume 40,000 times the usual dose to trigger a lethal response. Equal amounts of caffeine would lead to death quicker than marijuana. As of yet there are no documented cases implicating marijuana as the cause of death (Annas, 1997).

Recent interest has fueled progress in development of medicinal drugs. One such drug can be used topically to introduce the lipophilic substance into the body by using micro-emulsions and cyclodextrins to create greater solubility in aqueous solutions. This new form of application could result

in a less harmful method to utilize the beneficial medicinal properties of marijuana. (Green, 1998).

In addition, new forms of use can enable patients suffering from life threatening illnesses with symptoms that compromise their health and quality of life a way to control the pain. The discovery of the endocannabinoid system has led to an interest in the production of cannabinoid medications for treatment of symptoms such as nausea, vomiting, weight loss, and pain relief. Some of these synthetically produced cannabinoid medications have already been FDA approved which could prove to significantly enhance the quality of life for a patient suffering from an illness (Martin, Wiley, 2004).

While marijuana may have therapeutic benefits, a majority of the research conducted is on real users of the substance. This is a drawback because the dosage of THC in their systems are too high to properly assess what the outcome would be if the doses were administered and regulated. Even though there is promise in the study for the drug to be used medically, not enough case studies have been performed as of yet to examine all the parameters of the drug (Zuurman, et. al. 2009).

Conclusion:

Educated by the media and influenced by current social cultures, the author initially began this research project with the impression that marijuana was a benign and harmless substance. After doing extensive research on the subject, and reading a wealth of information, the author's views have been dramatically transformed.

The data concerning prenatal use as well as adolescent abuse of marijuana have proved to be quite conclusive with evidence demonstrating the harmful effects of the substance. There is a considerable amount of information available detailing a plethora of study methods and techniques which all yield similar adverse results. Although there seems to be promising research regarding marijuana as a medicinal therapeutic drug, as of now it is a very new and undeveloped method of treatment with lack of adequate information to ensure its long term safety.

While there is still a lot more research to be done, the information gathered concerning marijuana's adverse effects are too strong to ignore.

References:

Annas, G. (1997). Reefer madness--the federal response to California's medical-marijuana law. The New England Journal Of Medicine, 337, 435-439.

Barch, D.M., Smith, E. (2008). The cognitive neuroscience of working memory: relevance to CNTRICS and schizophrenia. Biological Psychiatry 64, 11–17.

Copeland, J., Gerber, S., Swift, W. (2006). "Evidence-based answers to cannabis questions," Australian National Council on Drugs, Canberra, Australia: New Millennium Print. 2-5.

Cornelius, M., Goldschmidt, L., Day, N., & Larkby, C. (2002). Alcohol, tobacco and marijuana use among pregnant teenagers: 6-year follow-up of offspring growth effects. Neurotoxicology And Teratology, 24, 703-710.

Devane, W., Hanus, L., Breuer, A., Pertwee, R., Stevenson, L., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., Mechoulam, R. (1992). Isolation and structure of a brain

constituent that binds to the cannabinoid receptor. Science (New York, N.Y.), 258, 1946-1949.

Diaz, J. (1997) How Drugs Influence Behavior. A Neuro-Behavioral Approach. Upper Saddle River, New Jersey: Prentice Hall.

Ellenhorn, M.J., and Barceloux, D.G. (1988). Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc., p. 680.

Fletcher, P. C., Honey, G. D. (2006). Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. Trends In Cognitive Sciences, 10, 167-174.

Fried, P., Watkinson, B., & Gray, R. (1992). A follow-up study of attentional behavior in 6 year old children exposed prenatally to marihuana, cigarettes, and alcohol. Neurotoxicology And Teratology, 14, 299-311.

Gorelick, D., Goodwin, R., Schwilke, E., Schwope, D., Darwin, W., Kelly, D., McMahon, R., Liu, F., Ortemann-Renon, C., Bonnet, D., Huestis, M. (2013). Tolerance to effects of high-dose oral δ9-tetrahydrocannabinol and plasma cannabinoid concentrations in male daily cannabis smokers. Journal Of Analytical Toxicology, 37, 11-16.

Green, K. (1998). Marijuana smoking vs cannabinoids for glaucoma therapy. Archives Of Ophthalmology, 116, 1433-1437.

Harbison, R., and Mantilla-Plata, B. (1972). Prenatal toxicity, maternal distribution and placental transfer of tetrahydrocannabinol. The Journal Of Pharmacology And Experimental Therapeutics, 180, 446-453.

Hazekamp, A., Ruhaak, R., Zuurman, L., van Gerven, J., and Verpoorte, R. (2006). Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol. Journal Of Pharmaceutical Sciences, 95, 1308-1317.

Hermanns-Clausen, M., Kneisel, S., Szabo, B. and Auwärter, V. (2012). Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction. doi: 10.1111/j.1360-0443.2012.04078.x.

Jutras-Aswad, D., DiNieri, J.A., Harkany, T., and Hurd, Y.L. (2009). Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci. 259:395–412.

Klugman, A., and Gruzelier, J. (2003). Chronic cognitive impairment in users of 'ecstasy' and cannabis. World Psychiatry: Official Journal Of The World Psychiatric Association (WPA), 2, 184-190.

Kogan, N., & Mechoulam, R. (2007). Cannabinoids in health and disease. Dialogues In Clinical Neuroscience, 9, 413-430.

Macdonald, C., Gregory, C. (1994). Drug and Alcohol Review. Informa Healthcare Volume 13, Number 2, pp. 209-216.

Martin, B., & Wiley, J. (2004). Mechanism of action of cannabinoids: how it may lead to treatment of cachexia, emesis, and pain. Journal Of Supportive Oncology, 2, 305-314.

Mechoulam, R., Deutsch, D. (2005). Toward an anandamide transporter. Proceedings Of The National Academy Of Sciences Of The United States Of America, 102, 17541-17542.

Meier, M., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R., McDonald, K., Ward, A., Poulton, R., Moffitt, T. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings Of The National Academy Of Sciences Of The United States Of America, 109, E2657-E2664.

Nahas, G., & Latour, C. (1992). The human toxicity of marijuana. The Medical Journal Of Australia, 156, 495-497.

Noland, J.S., Singer, L.T., Short, E.J., Minnes, S., Arendt, R.E., Kirchner, H.L., Bearer, C. (2005). Neurotoxicol Teratol. May-Jun; 27:429-38.

NORML Foundation (2013). NORML.org - Working to Reform Marijuana Laws. Retrieved January 5, 2013, from http://norml.org

Pertwee, R. G. (2006). Cannabinoid pharmacology: the first 66 years. British Journal Of Pharmacology, 147S163-S171.

Rachelefsky, G., Opelz, G., Mickey, M., Lessin, P., Kiuchi, M., Silverstein, M., & Stiehm, E. (1976). Intact humoral and cell-mediated immunity in chronic marijuana smoking. The Journal Of Allergy And Clinical Immunology, 58, 483-490.

Rais, M., Cahn, W., Van Haren, N., Schnack, H., Caspers, E., Hulshoff Pol, H., Kahn, R. (2005). Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. American Journal Of Psychiatry, 165, 490-496.

Reynolds, J. E. F., & Parfitt, K. K. (1993). Martindale: The Extra Pharmacopoeia. 30th ed. London; United Kingdom: The Pharmaceutical Press. ISBN 0-85369-300-5.

Richardson, G., Ryan, C., Willford, J., Day, N., & Goldschmidt, L. (2002). Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. Neurotoxicology And Teratology, 24, 309-320.

Sharman, J.L., Benson, H.E., Pawson, A.J., Lukito, V., Mpamhanga, C.P., Bombail, V., Davenport, A.P., Peters, J.A., Spedding, M., Harmar, A.J., (2013). IUPHAR-DB: updated database content and new features. Nucleic Acids Research, 41(Database issue), D1083-D1088. doi:10.1093/nar/gks960.

Silva, L., Zhao, N., Popp, S., & Dow-Edwards, D. (2012). Prenatal tetrahydrocannabinol (THC) alters cognitive function and amphetamine response from weaning to adulthood in the rat. Neurotoxicology & Teratology, 34, 63-71.

Solowij, N., Jones, K., Rozman, M., Davis, S., Ciarrochi, J., Heaven, P., Lubman, D., Yücel, M. (2011). Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. Psychopharmacology, 216, 131-144.

Wadsworth, E. K., Moss, S. C., Simpson, S. A., & Smith, A. P. (2006). Cannabis use, cognitive performance and mood in a sample of workers.Journal Of Psychopharmacology, 20, 14-23.

Wu, T., Tashkin, D., Djahed, B., & Rose, J. (1988). Pulmonary hazards of smoking marijuana as compared with tobacco. The New England Journal Of Medicine, 318, 347-351.

Zalesky, A., Solowij, N., Yucel, M., Lubman, D., Takagi, M., Harding, I., Lorenzetti, V., Wang, R., Searle, K., Pantelis, C., Seal, M. (2012). Effect of Long-Term Cannabis Use on Axonal Fibre Connectivity. Brain, 135, 2245-2255.

Zuurman, L., Ippel, A. E., Moin, E., & van Gerven, J. A. (2009). Biomarkers for the effects of cannabis and THC in healthy volunteers. British Journal Of Clinical Pharmacology, 67, 5-21.