A Review of Scientific Literature on the Relationship between Cannabis and Psychosis

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SUMMARY

Americans are using cannabis with increasing frequency to treat a wide variety of medical disorders. Despite the growth of medical cannabis use in the United States, many still have concerns about certain issues about cannabis safety. Cannabis has been shown through scientific evidence to be less dangerous than alcohol and pharmaceutical drugs. This is due to both a decrease in physical toxicity and psychological properties such as promoting destructive behavior and addictive tendencies when compared to other common drugs.

One of the questions of cannabis safety that scientific study has not revealed to be much safer than traditional drugs is the risk of psychosis. Although very rare, some people have experienced prolonged psychotic episodes after cannabis use. In a majority of these cases, the patients affected are typically adolescents with a family history of schizophrenia. The scientific evidence seems to indicate that the predominant component of cannabis, THC, can trigger psychosis is certain individuals, but another component of cannabis, CBD, can reverse psychosis.

Due to the complex relationship between cannabis and psychosis, we have provided a brief summary of our research below:

> A summary of the findings relating THC and psychosis: Large's study indicates a correlation between psychosis and adolescent cannabis use. Arseneault's study found a correlation as well, but described cannabis use as neither necessary nor sufficient to cause psychosis, but a component cause. Caspi's study found a strong correlation between adolescents with cannabis-induced psychosis and a specific genetic mutation, and postulates that genetic testing may indicate who is susceptible to cannabis-induced psychosis in the general population. Henquet's study found that most of the ability of cannabis to induce psychosis was found in patients with a predisposition to psychosis. Moore performed longitudinal studies and found that adolescent cannabis use correlated with higher probability of psychosis later in life.
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> A summary of the findings relating CBD and psychosis: Zuardi's study found that CBD was able to reverse psychosis caused by amphetamine and ketamine. Long's study found that CBD reversed psychosis brought on by dissociative drug MK-801. Leweke's study found found that CBD was as effective at treating schizophrenia as the FDA approved drug amisulpride with a much reduced profile of side-effects.

For a more detailed and annotated examination of the evidence from our research, we have provided a brief summary and analysis organized by author for our scientific publications relevant to the relationship between cannabis and psychosis:

Large's 2011 study performed a meta-data analysis on many studies and found a definite correlation between adolescent use of cannabis and a decrease in the age at onset of psychosis related disorders (mainly schizophrenia). The authors indicate that much of the raw scientific data derived from various studies did not indicate whether cannabis use predated the onset of psychosis, making the link a correlative rather than causal one. This means the authors cannot be sure if the psychosis increases the likelihood of cannabis use, or if the cannabis increases the likelihood of psychosis, an important distinction.

Large M, Sharma S, Compton MT, Slade T, Nielssen 0 (June 2011). "Cannabis use and earlier onset of psychosis: a systematic meta-analysis". Arch. Gen. Psychiatry 68 (6): 555-61. doi:10.1001/archgenpsychiatry2011.5. PMID 21300939

According to Arseneault's 2004 study, although cannabis use is correlated with earlier onset of psychosis in adolescents, they strongly indicate this phenomenon is only believed to occur in at-risk groups, such as family history of psychosis, or symptoms of psychosis predating cannabis use. This is difficult to prove because the mechanism of psychosis development in the brain is not well understood, and the role of cannabinoid receptors in this process is even less well known. An overall acceptance of the fact that cannabis use can exacerbate at- risk (of psychosis) youths pervades the literature on the subject. The author's language best describes the exact nature of the relationship: "Cannabis use appears to be neither a sufficient nor a necessary cause for psychosis. It is a component cause, part of a complex constellation of factors leading to psychosis.

Arseneault L, Cannon M, Witton J, Murray RM (2004). "Causal association between cannabis and psychosis: examination of the evidence". The British Journal of Psychiatry 184(2): 110-117. doi:10.1192/bjp.184.2.110. PMID 14754822

Caspi et al's 2005 study correlated an earlier onset of psychosis in cannabis users with a specific polymorphism in the catecholamine o-methyltransferase gene, specifically the Valine-158 allele was the most likely to be correlated with psychotic symptoms. This indicates that those at risk may potentially be informed through genetic testing. The paper goes so far as to state that cannabis users with a homozygous Methionine-158 genotype will have no such adverse effects from cannabis consumption. Alternatively a study conducted by Zammit et al in 2007 concluded that cannabis use had no modulatory effects on psychotic symptoms or on either valine or methionine allele catecholamine o-methyltransferase.

Caspi A, Moffitt TE, Cannon M, McClayJ, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW (2005). "Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction". Biological Psychiatry 57 (10): 1117-27. doi:10.1016/j.biopsych.2005.01.026.PMID 15866551

The debate over cannabis' causal connection to schizophrenic onset in adolescents has been ongoing in the scientific community for some time, and fortunately has produced a wealth of literature, and more importantly, empirical evidence on the subject. For example, Henquet's 2005 study concludes, "Cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis."

Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van OsJ (2005)."Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people". BMJ 330 (7481): 11-0. doi:10.1136/ bmj.38267.664086.63.PMC 539839. PMID 15574485

Conversely, Moore's 2007 longitudinal study concluded with a very different tone: "The evidence is consistent wit the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. The uncertainty about whether cannabis causes psychosis is unlikely to be resolved by further longitudinal studies such as those reviewed here. However, we conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing psychotic illness later in life"

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007). "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review". The Lancet 370 (9584): 319-28. doi:10.1016lSOl40-6736
(07)61162-3. PMID 17662880

CBD AND PSYCHOSIS

Zuardi et al's 2006 study investigated CBD's anti-psychotic nature, and revealed its effects to be broadly anxiolytic and anti-psychotic. Although THC's ability to induce psychotic-like symptoms seems to suggest CBD's antagonist properties at the cannabinoid are solely responsible for its anti-psychotic properties, CBD's ability to reverse anxiety in cannabinoid-naive subjects suggested otherwise. Amphetamine and ketamine induced psychosis in mice, which effect the dopaminergic neurons (D2) and glutaminergic neurons (NMDA) respectively, were both reversed by CBD administration. This indicates that CBD's anti-psychotic effect may have a broader pharmacological basis than Cbl, D2, or NMDA antagonism alone. This is consistent with Campos et al's 2012 theory that the TRVPl receptor (of which CBD is an agonist) is responsible for contributing to CBD's anti-psychotic effects. Additionally, Zuardi's team found that CBD was both a safe and efficacious alternative treatment for schizophrenia which was well tolerated.

Zuardi AW, Crippa JA, HallakJE, Moreira FA, Guimaraes FS (April 2006)."Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug". Braz. J. Med. Biol. Res. (Review) 39 (4): 421-9. doi:10.1590/SOl00-879X2006000400001.PMID 16612464

Long et al's 2005 study investigated CBD's ability to reverse MK—801 (an NMDA antagonist) induced psychotic symptoms in mice. CBD did reverse the effects of MK—801, but when co-administered with capsazepine, a TRVPl antagonist, CBD's effects disappeared. This evidence strongly indicates TRVPl's role in CBD treatable psychosis, and potentially its interrelation to several other neural systems (such as the NMDA receptor seen here, or the D2 and C81 neural systems cited in Zuardi 2006 and Campos 2012).

Long, L. E.; Malone, D. T.; Taylor, D. A. (2005). "Cannabidiol Reverses MK-801-lnduced Disruption of Prepulse Inhibition in Mice". Neuropsychopharmacology 31 (4): 795-803.doi:10.1038/sj.npp.1300838. PMID 16052245

Leweke et al's 2012 study performed a clinical trial with schizophrenic patients comparing the efficacy of CBD versus amisulpride. The study cited previous work's by Lewek where the elevated levels of synpatic anandamide (a endocannabinoid ligand for Cbl receptors in the brain) correlated with CBD plasma levels, indicating CBD's ability to inhibit enzymatic degradation of anandamide (through Fatty Acid Amide Hydrolase or FAAH). The study found that CBD was equally effective as amisulpride (a drug that antagonizes D2 and D3 dopamine receptors) at treating psychotic symptoms of schizophrenia, but with a much reduced profile of side-effects. These findings indicate that proper use or drug-assisted optimization of the transmission of endocannabinoids can preclude harsher dopamine antogonist drug therapy. With relation to THC's rare but significant tendency to induce psychosis in

adolescents, the question arises why does THC triggering the C81 receptor cause psychosis while anandamide triggering the same Cbl receptor seem to reverse psychosis? A factor to consider is that the bodies natural endocannabinoids are part of feedback loops that stop excessive transmission across a synapse. If the synapses effected by this feedback loop are insufficient, CBD's inhibition of endocannabinoid breakdown would assist the body in transmitting its desired signal. When THC is ingested and enters the brain, the C81 receptors are triggered randomly and uniformly, not reflecting an organized response by the neural network, and in fact imposing a uniform stimulus on a complex system and causing a degree of chaos and interference. When anandamide is assisted by CBD, the neural network's response is appropriately effected, and the natural feedback built into the endocannabinoid system can prevent over stimulation of CB receptors at any one synapse, something not available when ingesting THC. This also applies to the synaptic specificity, because THC flows through the blood and cerebro-spinal fluid, it will not target the correct synapses, but rather target them all. Because anandamide is released within the synapse it is needed in, by the neuron that wishes to transmit the signal, it cannot overwhelm other CB receptor containing synapses. These factors may reconcile the seemingly paradoxical relation between psychosis, CB1 receptors, and THC and CBD's apparently opposite effects on the same receptor.

Leweke, FM; Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, KlosterkotterJ, Hellmich M and Koethe D. (2012). "Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia". Translational Psychiatry 2 (3):
e94-.doi:10.1038ltp.2012.15. PMC 3316151. PMID 22832859