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Cannabis Induced Psychopathology

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Abstract

The recent trend towards legalization and commercialization of marijuana in the US has resulted in a significant drop in the perceived risks of cannabis use among all age groups. Thus, legalization has further advances the common misperception that cannabis abuse and dependence are generally safe and devoid of neuropsychiatric sequelae. Yet there are numerous acute, as well as numerous long-term neuropsychiatric consequences of cannabis use. In addition to acute psychosis and agitation, this review will discuss the long-term issues of cognitive decline, permanent psychotic disorders, syndromes of prolonged depersonalization, as well as psychological and physical dependence, and related withdrawal symptoms.

Cannabis use, particularly repeated exposure, is an established contributory cause of schizophrenia by way of a classic gene-environment interaction, with the vulnerabilities associated with cannabis-induced schizophrenia involving multiple genes. There is also evidence that in utero cannabinoid exposure will impair brain maturation in developing infants and predispose them to neurodevelopmental disorders during childhood.

This summary will inform clinicians of the most prevalent consequences associated with cannabis abuse and dependence, and better equip them to educate patients as to these risks. Further, there are treatments that may help patients achieve abstinence, and even neuroprotective strategies to employ in cases of new-onset cannabis-induced psychosis, as well as for cases of in utero exposure.

Keywords: Schizophrenia; Cannabis abuse; Paranoia; Anxiety; Psychosis

Acute Cannabis Induced Psychopathology

For some individuals, cannabis use does not produce a calming sensation; rather, it will induce anxiety and, in some, panic attacks [1]. Numerous case reports indicate that typical panic attack symptoms often present with intense depersonalization [2]. Though possibly related to an underlying genetic vulnerability, the specifics of this interaction have yet to be discerned, however, individuals who do experience panic and anxiety symptoms during abuse are more likely to abstain from cannabis in the future [3].

The mechanism of cannabis-induced paranoia and hallucinations while abusing is believed to involve the relationship between dopamine activity and endocannabinoid transmitters. Stimulation of D2 receptors in the striatum will result in the synthesis and release of endocannabinoids, which act in a retrograde fashion to inhibit GABA and glutamate activity. Researchers have speculated that due to the number of key physiological processes within the striatum dependent on D2 to endocannabinoid signaling, this process is vital for normal functions of the striatum in health [4].

They further theorized that the reason antipsychotics are less effective for acute cannabis-induced psychosis is because they exert their effects through D2 blockade, while THC enters the pathway "downstream" from D2 receptors [4]. Further, acute psychosis is often a harbinger of future psychopathology, as those who experience cannabis-induced psychosis have an eight-year cumulative risk of 46% for eventually being diagnosed with schizophrenia (compared to the 30% risk associated with amphetamine-induced psychosis) [5].

In cases of THC toxicity, patients will experience impairments in attention and concentration, short-term memory deficits, as well as impaired executive functioning [6,7]. The most severe adverse effects occur after higher doses, or high potency preparations, are ingested, and include nausea, tachycardia, blood pressure changes (hypertension and/or orthostatic hypotension), conjunctival injection, dry mouth, ataxia, slurred speech, nystagmus, manic-like euphoria, perceptual changes, psychomotor impairment, mental status changes consistent with delirium, extreme anxiety, panic attacks, and myoclonic jerking [8]. Treatment of toxicity is largely supportive, providing a low stimulation environment and benzodiazepines are usually administered.

Cognitive Decline

Though cannabis-induced a motivational syndrome is still debated, the evidence that persistent cannabis use will result in long-term neurocognitive deficits is becoming clearer. It has now been established that white matter connectivity is affected in early-onset users of cannabis, and more recent data supports the probability of this sequelae in early users [9,10]. Further, cannabis-induced white matter changes are indeed directly correlated with objective cognitive impairment [11].

A recent a prospective cohort study of 1,037 individuals followed from birth (1972/1973) to age 38 examined the specifics of a possible cannabis-induced cognitive decline. Cannabis use was ascertained by interviews at ages 18, 21, 26, 32 and 38. Neuropsychological testing was first conducted at age 13, before initiation of cannabis use, and again at age 38, after a pattern of persistent cannabis use had been reported.

Persistent cannabis use was indeed associated with a broad neuropsychological decline, even after controlling for educational background. The cognitive impairments were primarily associated with adolescent-onset cannabis users, with the more persistent users demonstrating the greatest decline. Further arguing for the impact cannabis has on the developing brain, cessation of cannabis did not fully reverse the neuropsychological decline among adolescent-onset users. The authors noted that their "findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents" [12].

Neuroimaging studies in long-term cannabis users have also found structural and neurophysiologic changes. Magnetic resonance imaging in one study demonstrated that long term, heavy use was associated with significantly reduced hippocampus and amygdala volumes (regions with high concentrations of cannabinoid receptors) [13]. The authors also noted that a greater cumulative cannabis exposure was associated with more severe volume reductions.

A recent positron emission tomography study in heavy cannabis users found a variety of abnormalities even after a 25 day period of abstinence, the authors felt translated into the clinical manifestation "that very heavy users of marijuana have persistent decision-making deficits and alterations in brain activity. Specifically, the heavy marijuana users may focus on only the immediate reinforcing aspects of a situation (i.e., getting high) while ignoring the negative consequences" [14].

A unique transcranial Doppler sonography study found that chronic marijuana use was associated with increased cerebrovascular resistance, believed mediated through changes in CNS blood vessels or in brain parenchyma, a possible contributory mechanism for the cognitive deficits observed in persistent marijuana users [15]. Further, structural brain changes associated with cognitive impairment are more likely to occur in users of high-potency cannabis [16].

Depersonalization Disorder

Numerous case reports and case series document that depersonalization may be induced by cannabis use, and in some users, this effect will persist and result in the eventual diagnosis of depersonalization disorder [17]. The patients at highest risk are those who abuse high potency varieties or synthetic cannabinoids, and those who consume high doses during adolescence. Other risk factors include experiencing cannabis-induced panic attacks and/or transient psychosis while using [18,19].

The majority of cases are male, and most often begin between the ages of 15 and 19, though adult occurrences are not rare, and cases have also been reported after single-use exposure to high potency THC [19-21].

NMDA (N-methyl-D-aspartate) receptor antagonists (such as ketamine) will readily induce depersonalization and derealization. NMDA receptors are widely distributed in the cortex, hippocampus and amygdala, and known to mediate associative processes. It has recently been shown that CB1 receptors regulate NMDA receptors at the postsynaptic membrane and the mechanism for depersonalization is believed to involve the complex relationship between cannabinoids and NMDA regulation [22].

The sensations of depersonalization and derealization may be difficult for patients to articulate and is often anxiety provoking, in fact, sufferers often present as benzodiazepine seekers. Though benzodiazepines may temporarily lessen the anxiety associated with these sensations, they are not indicated as treatment. Case reports indicate that serotonin reuptake inhibitors may be of benefit and naltrexone has provided relief of symptoms when studied in depersonalization disorder [20,23].

Cannabis Induced Psychosis and Cannabis-Induced of Schizophrenia

Acute intoxication, or simply use of cannabis in vulnerable individuals, has long been associated with paranoia and other temporary psychotic symptoms and those who experience acute psychotic symptoms are further expected to be at risk for developing a permanent psychotic disorder [5]. Multiple studies have confirmed the connection between cannabis use and the development of schizophrenia, especially in adolescent users. In general, heavy users, and those who abuse high THC content or synthetic varieties, are at the greatest risk [24]. The gene-environment interaction is becoming clear and estimates range from 10 to 15% of schizophrenic cases are attributable to THC exposure or dependence, and it has been further estimated that the prevalence of schizophrenia would drop by 8% if abstinence from marijuana were a public health priority [25].

A recent study found that patients experiencing first-break psychotic episodes were twice as likely to have smoked cannabis for over 5 years and they were 6 times more likely than controls to be daily users. In this same study, 78% of the first-break patients versus 37% of the control group were abusing high potency, or synthetic cannabis [26]. A meta-analysis of 83 observational studies of schizophrenics found that the onset of illness occurred much earlier (2.7 years) in cannabis using patients compared with those schizophrenics who had never abused [27].

It is well established that schizophrenia is highly heritable: twin studies indicate the magnitude of genetic influence to be as high as 83% [28]. Thus, for a percentage of schizophrenics, the environmental risk factor of cannabis exposure interacted with their genetic vulnerabilities to increase the risk of the occurrence of a schizophrenic disorder. Patients and their families need to be aware that the consequences of cannabis use can be life-long and disabling for those individuals who possess these underlying genetic risks.

Of course, cannabis use is a common factor involved in symptom exacerbation, relapses, hospitalizations, and poor compliance in patients with established schizophrenia, and these consequences are also common for patients with bipolar and schizoaffective disorders [29].

Mechanisms of Cannabis Induced Psychosis

THC (delta-9-tetrahydrocannabinol) is the major psychoactive component of marijuana, exerting it activity by the stimulation of the CB1 receptors. Synthetic cannabinoids may be 800 times more potent than TCH at the CB1 receptors [30]. CB1 receptors are widely distributed through the brain, the prefrontal cortex, basal ganglia,

hippocampus, and amygdala. CB1 receptors are primarily expressed on glutamate and GABA-ergic terminals. Upon stimulation, they act to reduce presynaptic glutamate or GABA release.

The dopaminergic neurons in the ventral midbrain do express CB1 receptors and exogenous cannabinoids will no doubt alter the balance of inhibition and excitation reaching dopamine cells. The most commonly observed effect is the increased firing of these neurons and subsequent elevations of dopamine in the forebrain, thus triggering the principle mechanism of psychosis.

Under controlled conditions, THC and synthetic cannabinoids elicit psychotic symptoms in a percentage of healthy volunteers [31]. Further supporting the gene-environment interaction, THC does not induce a significant increase in striatal dopamine in healthy normal, but does so in schizophrenics and relatives of schizophrenics [4].

Of the 85 active cannabinoids identified in marijuana, only cannabidiol (CBD) is believed to possess antipsychotic properties. Not only has higher content cannabidiol marijuana been shown to be less commonly associated with psychotic reactions, small-scale clinical studies of CBD in patients with psychotic symptoms further enforce the potential of CBD as an eventual antipsychotic agent [32,33]. Data implies that CBD may counteract the psychotic symptoms and cognitive impairment associated with acute THC administration. In addition, CBD may lower the risk for developing cannabis-induced psychosis. These effects are possibly mediated by the opposite effects of CBD and THC, specific to dopaminergic pathways, in the striatum, hippocampus, and prefrontal cortex [34].

Unlike marijuana available in past decades, as when the TCH content was <1% in the 1970's, and there was at least a 1% cannabidiol content, there is virtually no cannabidiol in current plants, which have been bred to contain >12% THC. Thus, current varieties have an estimated seven-fold increase in potency regarding the potentially psychosis-inducing component and 0% of the potentially antipsychotic CBD component [35].

The Genetic Basis of Cannabis-Induced Schizophrenia

The earliest gene-environment connection was thought to involve the COMT, or catechol-O-methyltransferase gene. Since the COMT enzyme metabolizes dopamine and other neurotransmitters, and is relatively restricted in its effects to the prefrontal cortex, it is particularly relevant to schizophrenia. The patients at greatest risk of cannabis-induced schizophrenia were determined to be adolescent users and who also possessed the Val phenotype coding for the COMT enzyme [36]. Val being the "high activity" allele. Yet the lack of replicated findings and a recent meta-analysis argue that this particular association is now in doubt [4].

More recent findings implicate the AKT1 gene. AKT1 is also known as Protein kinase B (PKB), and it plays a key role in multiple cellular processes such as apoptosis, glucose metabolism, cell proliferation, transcription, and cell migration. Since it inhibits apoptosis (the programing of DNA for cell death), the AKT1 gene is therefore critical in cellular survival pathways. The initial AKT1 findings were replicated in a study showing the carriers of the "C/C" genotype had a sevenfold increase in the odds of psychosis when exposed to cannabis compared with "T/T" carriers. A 2015 study of 222 first-break psychotics compared with 228 controls not only confirmed the AKT1 link, but further discovered that there was also an interaction with a dopamine receptor genotype. Individuals carrying the dopamine receptor D2 (DRD2) "T" allele, and those carrying the AK1 "C" allele were both at increased risk of developing cannabis-induced psychosis, particularly in the presence of both risk genes among daily cannabis users [37].

In Utero Exposure

The endocannabinoid system (ECS) includes CB receptors, endogenous ligands (endocannabinoids), associated enzymes (for synthesis and degradation), and transporter molecules. And the ECS is known to play key roles from the earliest embryonic stages through postnatal development. In fact, the endocannabinoid 2-arachidonoylglycerol is also present in maternal milk. As a recent review summarized "During early gestation, successful embryonal passage through the oviduct and implantation into the uterus require critical enzymatic control of the endocannabinoids. During fetal life, endocannabinoids and the cannabinoid CB1 receptor are important for brain development, regulating neural progenitor differentiation and guiding axonal migration and synaptogenesis." And further, postnatally, CB1 receptor activation by 2-arachidonoylglycerol appears to play a critical role in development and nutrition [38].

Not surprisingly, maternal marijuana consumption, i.e., perinatal manipulation of the ECS, alters development and neurotransmitter functions in the child. The sequelae associated with prenatal cannabis exposure have been compared to the many effects of prenatal stress, "which may suggest that prenatal stress impacts on the ECS and that vice versa prenatal cannabinoid exposure may interfere with the ability of the fetus to cope with the stress" [38].

Expectant mothers and those considering pregnancy should be made aware of these risks during routine pre-pregnancy consultation and prenatal care.

Further Treatment and Neuroprotective Options

There is evidence that n-acetyl cysteine (NAC), the amino acid available over-the counter may help cannabis-dependent users abstain [39]. This recommendation has the added benefit of leading to CNS antioxidant production. NAC is essentially a prodrug for l-cysteine, which is a precursor to the CNS antioxidant, glutathione. NAC is a natural compound, and generally recognized as safe.

Once cannabis-induced psychosis occurs, abstinence is a must. Antipsychotics are also necessary, and their use early in the course of a psychotic illness may provide neuroprotective value [40]. Though very early in the process of data-gathering, the current evidence for omega-three treatment for neuroprotection, and helping to prevent the conversion from schizophreniform disorder to schizophrenia, is also compelling [41]. Again, this specific recommendation is generally recognized as safe.

Further, strategies that lower CNS homocysteine (HCY) levels are also being studied at present in hopes of demonstrating neuroprotective value. HCY reduction may also contribute to helping prevent the eventual conversion from a drug-induced psychosis, or a schizophreniform disorder, to chronic schizophrenia. Though long understood as a mere finding associated with the diagnosis, new evidence indicates that HCY is also involved in the pathophysiology of schizophrenia [42]. Newer, prescription B vitamins (in their fully metabolized forms) have been shown to reliably lower HCY in psychiatric patients, thus offering another natural, safe and potentially neuroprotective option for patients at risk for permanent psychotic disorders [43].

In cases of in utero exposure, once again, immediate and continual abstinence is the first priority. No specific detox medications are needed, but a daily prenatal vitamin, preferably one designated for high-risk pregnancies (formulated for optimal neuroprotection) should be utilized.

Summary

A 2013 study found that 7.5% of Americans 12 and older reported using marijuana within the month prior to the survey, which represented an increase from 5.8% of respondents in 2007 [44]. As the prevalence of marijuana use increases, neuropsychiatric consequences are also expected to increase. Far from being harmless, cannabis abuse and dependence may result in a variety of neuropsychiatric illnesses, the most devastating being cannabis-induced schizophrenia, and the CNS neuronal alterations caused by prenatal exposure. Clinicians have a duty to educate patients and the public on the dangers described above and to consider neuroprotective strategies where indicated.

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