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# Cannabis-Induced Hypodopaminergic Anhedonia and Cognitive Decline in Humans: Embracing Putative Induction of Dopamine Homeostasis

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Over years, the regular use of cannabis has substantially increased among young adults, as indicated by the rise in cannabis use disorder (CUD), with an estimated prevalence of 8.3% in the United States. Research shows that exposure to cannabis is associated with hypodopaminergic anhedonia (depression), cognitive decline, poor memory, inattention, impaired learning performance, reduced dopamine brain response-associated emotionality, and increased addiction severity in young adults. The addiction medicine community is increasing concern because of the high content of delta-9-tetrahydrocannabinol (THC) currently found in oral and vaping cannabis products, the cognitive effects of cannabis may become more pronounced in young adults who use these cannabis products. Preliminary research suggests that it is possible to induce 'dopamine homeostasis,' that is, restore dopamine function with dopamine upregulation with the proposed compound and normalize behavior in chronic cannabis users with cannabis-induced hypodopaminergic anhedonia (depression) and cognitive decline. This psychological, neurobiological, anatomical, genetic, and epigenetic research also could provide evidence to use for the development of an appropriate policy regarding the decriminalization of cannabis for recreational use.

**Keywords:** cannabis use disorder, depression, anhedonia, neuroanatomic alterations, reward deficiency syndrome, genetic testing, pro-dopamine regulation, dopamine homeostasis

## PREVALENCE

Cannabis is regarded as the most abused illicit drug in the world today. An estimated 150–200 million people use cannabis regularly, and a relatively common disorder, known as cannabis use disorder (CUD), has an estimated prevalence of 8.3% in young adults in the United States (1, 2). A recent survey of 482 young college students, ~19–20 years, found that 29% of students vaped cannabis. From this survey, men from high socioeconomic status (SES) vaped higher cannabis amounts than men 13–14 years from lower SES status and women (3). Between 2000 and 2016, the lifetime and daily use of cannabis among 12th graders was 44 and 6%, respectively. In 2019, 8th graders' ~13–14 years, past-year use was 11.8%, and past-month use was 6.6%, 28.8% of 10th graders had used marijuana in the past year and 18.4% in the past month. Among 12th graders, ~17–18 years, rates of cannabis use grew to 35.7% during the previous year and 22.3% in the previous month. Reports of daily and near-daily use were 6.4%. Almost 4% of 12th grader teens vape cannabis products daily (NIH What is the scope of marijuana use in the United States? Marijuana Research Report, <https://www.drugabuse.gov/> [accessed October 28, 2020]).

More importantly, there is increasing concern by the addiction medicine community that because of the high content of delta-9-tetrahydrocannabinol ( $\Delta$ 9-THC), (the chemical that causes the high) currently found in edibles and vaping cannabis vaping products [up to 90%; <https://www.marijuanabreak.com/90-percent-thc-weed>, (accessed January 20, 2020)], the chronic cannabis users may develop more severe hypodopaminergic-anhedonia (depression) and cognitive decline. Incidentally, other serious respiratory and pulmonary consequences, including chronic obstructive pulmonary disorder (COPD), have also been reported among those who use e-vaping devices (4).

## CANNABIS AND NEUROANATOMIC ALTERATIONS AND COGNITION

Cannabidiol (CBD) can ameliorate the effects of THC and protect the brain from damages, possibly through CB1 antagonism (5). These psychophysiological damages include dose-dependent psychotic cognitive and behavioral symptoms (6) and observed from several human structural neuroimaging studies frequency of use dependent reductions in gray matter volumes. The reductions occur in the medial temporal cortex, orbitofrontal cortex, temporal poles, parahippocampal gyrus, and insula. Chronic cannabis users also display significant neuroanatomic alterations in the medial temporal, frontal cortex, cerebellum (7), and the fusiform gyrus, temporal pole, superior temporal gyrus, and occipital cortex (8).

A top area of concern, especially in young developing adults, is the damaging effect of high doses of  $\Delta$ 9-THC and consequent cognitive impairment. According to Floresco et al. (9) and Lorenzetti et al. (8), the neuroanatomic alterations in the prefrontal-hippocampal function and subsequent down-regulation of CB1 receptors may result in cognitive decline/working memory, decision-making, and inhibitory

control in chronic cannabis users. Cannabinoid type 1 receptors (CB1) associated with motivational, emotional, and affective processing (10) are usually abundant in these areas, so upregulation of CB1 receptors may positively affect THC-induced brain damage. Notably, these cognitive effects may return to normal after 4–6 weeks of abstinence from cannabis (11, 12).

## THE SYNAPTIC MECHANISMS UNDERLYING THC-INDUCED ANHEDONIA AND COGNITIVE DEFICITS

In adult cannabis users, brain activation decreases in the middle temporal gyrus, insula, and striate area and increases in the superior and posterior transverse temporal and inferior frontal gyri and middle temporal gyrus. While activation in adolescents increases in the inferior parietal gyrus and putamen compared to healthy controls (13). Research suggests that functional alterations in these areas are neuroadaptive changes in cannabis users and may be compensatory (13).

## CANNABIS AND DOPAMINERGIC FUNCTION

Chronic cannabis usage, including in adolescents, has also significantly reduced striatal dopamine release causing (hypodopaminergia) and associated poor memory, inattention, and impaired learning performance (14). Chronic use of cannabis observed with [18F]-DOPA PET found reduced brain dopamine synthesis and subsequently attenuated reward sensitivity, motivation, and induced apathy. It is noteworthy that the 9/9 allele polymorphism carriers have high D2/D3 receptor availability (due to higher dopamine re-absorption rates) compared to carriers of the 10/10 alleles in early-onset heavy cannabis users (15). The carriers of the 7R DRD4 polymorphism are likely to experiment with cannabis more than the non-carriers. According to Volkow et al. (16), among cannabis users, there is a reduced dopamine brain response linked to the emotionality and severity of the addiction. Cannabis users also show inversely correlated dopamine reactivity with higher negative emotionality scores relative to controls (17). There is some evidence that suggests large doses of  $\Delta$ 9-THC increase dopamine release by inhibiting VTA GABAergic activity (18). This effect may translate to an increased fear reaction in cannabis users. In animal experiments (19), the repeated administration of  $\Delta$ 9-THC induced depressive-like symptoms, including prolonged anhedonia due to CB1 type receptors' impairment and dopaminergic alterations in the mesolimbic region. This  $\Delta$ 9-THC induced dysfunction in animals associates with attenuated anandamide signaling. Interestingly, the subjects with CUD diagnosis and no baseline depressive symptoms were at the follow-up, four times more likely (age-adjusted) to have depressive symptoms than those with no CUD diagnosis (20).

In the past, the chronic use of cannabis of low potency (2–4%  $\Delta$ 9-THC) did not associate with significant neuroanatomic alterations, psychosis, or even depression. However, as the

mean  $\Delta 9$ -THC concentration has increased substantially over the last 10 years, from 8.9 to 17.1% by 2017 (21), the use of cannabis products such as pastes, gummies, and e-vaping devices with still higher concentrations of  $\Delta 9$ -THC, reported as high as 90%, may result in a higher degree of hypodopaminergia, associated poor memory, inattention, and impaired learning performance in chronic cannabis users, especially among adolescents with cannabis use disorder. Thus, the brain changes and symptomatology that signify chronicity depend on potency and duration, frequency of use; smoking cannabis daily multiple times per day.

## BALANCING DOPAMINE FUNCTION WITH PRECISION PRO-DOPAMINE REGULATION

The functional neuroimaging techniques, such as resting-state functional magnetic resonance imaging (rsfMRI), have shown that acute exposure to cannabis reduces the neuronal activity in the nucleus accumbens (NAc) and prefrontal cortex (PFC), anterior cingulate gyrus (ACG), striatum, and thalamus. In contrast, chronic cannabis exposure increases the rsfMRI in these brain regions, and in adolescents' chronic use of high  $\Delta 9$ -THC content cannabis results in impaired motivation with depression, anhedonia, low academic achievement, and reduced functional connectivity in the brain reward circuitry (22, 23). The primary neurochemical insult is an altered dopaminergic function across mesolimbic pathways requiring neurotransmitter balance across the brain reward system. Nestor et al. (24) found that in chronic cannabis users (with an average of 6.1 [range = 2.5–17] lifetime years of cannabis use and with the consumption of 7,258-lifetime cannabis joints), there is an increased ventral striatal (VS) blood-oxygen-level-dependent (BOLD) response to stimuli predicted potential non-drug rewards. Importantly, VS hyperactivity is seen during reward anticipation associated with years of cannabis use and the lifetime estimation of numbers of cannabis joints consumed. Another known impairment related to chronic cannabis use relates to compulsive drug use with NMDA receptor-dependent synaptic depression located at the ventral tegmental area (VTA) linked to dopamine circuitry. Chronic cannabis exposure also activates VTA cannabinoid CB1 receptors and reduces transient neurotransmission at VTA local Glu-DA synapses by activating NMDA receptors and subsequent endocytosis of AMPA receptor GluR2 subunits (25).

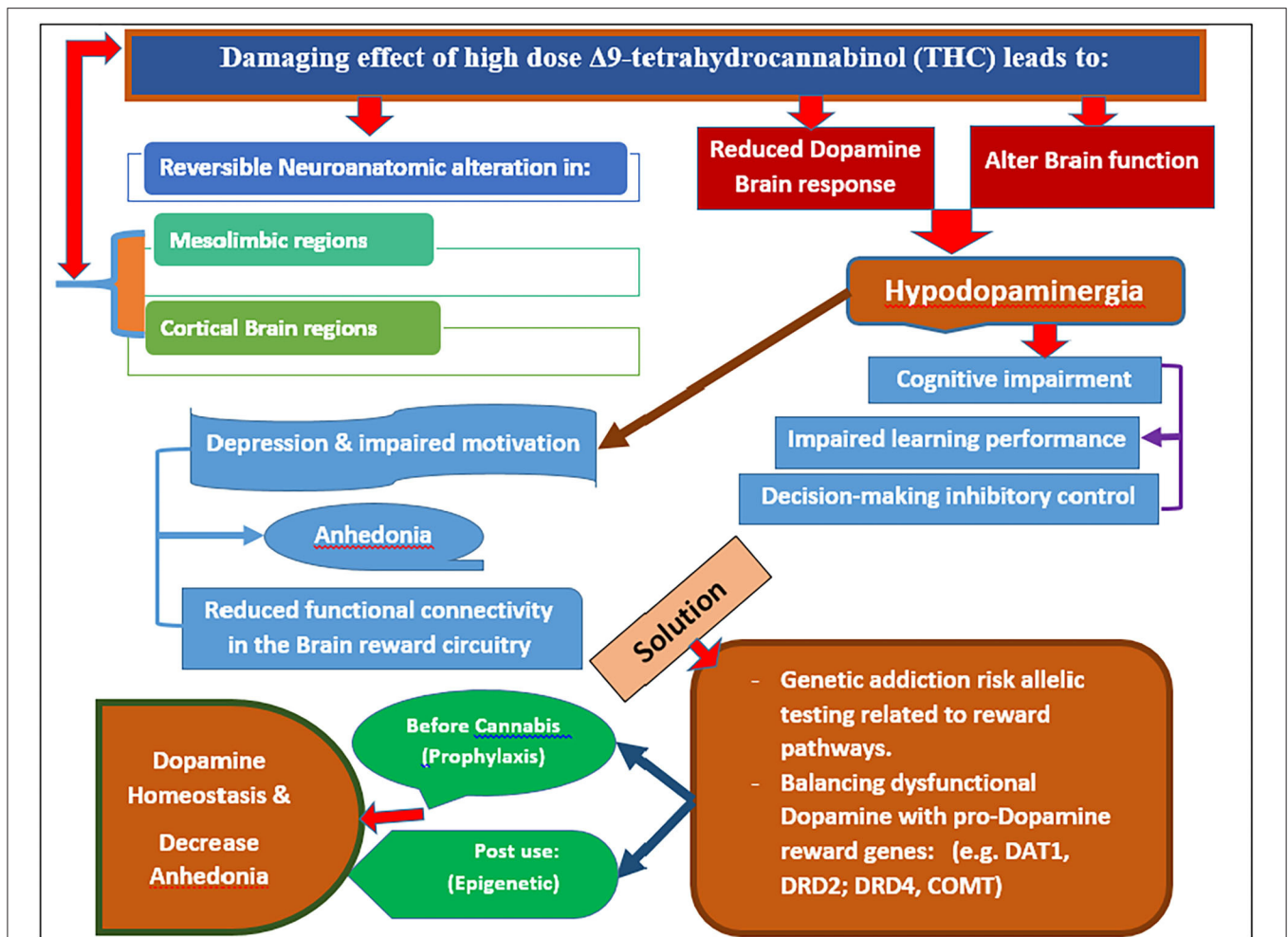
This evidence provides possible new targets in obviating chronic addiction learning, specifically with chronic cannabis use in humans. Dopamine augmentation is difficult to achieve, especially after the development of a substance use disorder (SUD). Vigorous physical exercise, like Eminem, TMS, and nutraceuticals, have been proposed as viable options. Our proposal herein of incorporating genetic risk allelic testing related to reward pathways along with potential induction of dopamine homeostasis seems logical. This concept takes on even more importance when we consider that the onset and peak use of cannabis occur during brain development in teenagers and, as such, represents an unwanted window of liability (26, 27). The onset of cannabis use begins in the mid-teens and peaks by the

age of 25, with the development of cannabis use disorder between 15 and 20. In order to either prevent or treat the high dose  $\Delta 9$ -THC-induced hypodopaminergic anhedonia and cognitive decline, it may be possible to combine the non-invasive testing for the genetic addiction risk score (GARS) with pro-dopamine regulation and restore the dopamine function (26–58). A novel model (Figure 1) espouses a reasonable biphasic approach; a short-term blockade followed by long-term dopaminergic upregulation with KB220Z\* primarily for reward deficiency syndrome (RDS) behaviors (29–38).

**“\*KB220Z Components, The most recent variant of KB220Z (powdered form), is composed of the following ingredients: Vitamin B6, 10 mg (500%); Thiamine, 15 mg (1,033% of Daily Value); and Chromium poly nicotinate, 200 mcg (166%). A fixed-dose of synaptose is included as well, which is a combination of amino acids and herbs that contains DL-Phenylalanine, L-Tyrosine, Passion-Flower Extract; a Complex containing Arabinogalactans, N-Acetylglucosamine, Astragalus, Aloe Vera, Frankincense Resin, White Pine Bark Extract, and Spirulina; Rhodiola; L-Glutamine; 5-Hydroxytryptophan (5-HTP); Thiamine Hydrochloride; Pyroxidal-5-phosphate and Pyridoxine HCl, CoQ10, NADH, and N-Acetyl Cysteine (NAC); (59). The powder was manufactured by Cepham, Inc. (New Jersey)”**

However, in chronic cannabis-using adolescents, the goal would be to enhance brain reward functional connectivity [measures the degree of synchrony of the BOLD time-series between different brain regions] and connectivity volume [Voxel-based morphology (VBM)], attenuate depression-like symptoms (anhedonia), and target stress-like anti-reward drug dependence symptoms. Using fMRI of both naive animals (60) and heroin abstinent subjects (61), we confirmed blood-oxygen-level-dependent (BOLD) activation of dopaminergic reward pathways and recruitment of dopamine neuronal firing with KB220Z. These types of fMRI results provide some evidence for dopaminergic activation.

Millions of individuals worldwide struggle to combat their frustrating and even fatal romance with getting high daily. The neuroscience community conducts and funds incredible research using sophisticated molecular-genetic applied technology in animal experiments and humans using neuroimaging to advance our understanding of brain reward circuitry's complex functions that play a vital role in the expressed symptoms found in addictions. Although dopamine is known as a major neurotransmitter involved in addictions, many disagree about how to deal with dopamine dysregulation clinically to prevent and treat addictive disorders, including cannabis use disorder (CUD). An alternative approach could include two phases; a brief blockade followed by stable dopaminergic upregulation. The treatment goal would be to augment brain reward functional connectivity volume by targeting reward deficiency and the stress-like anti reward symptomatology of addiction. These phenotypes can be characterized using the Genetic Addiction Risk Score (GARS). Dopamine homeostasis may thus be achieved via “Precision Addiction Management” (PAM)<sup>®</sup>, the customization of neuronutrient supplementation based on the GARS test result, along with a behavioral intervention (29).



**FIGURE 1** | It is a Model proposed for combatting chronic use of potent cannabis and anhedonia (Original figure Blum 2020). Note: Potency of cannabis may be as high as 90% THC in gummies and vaping products.

Dopaminergic homeostasis could be achieved by genetic testing for addiction risk and administering precursor amino acid and enkephalinase inhibitory, non-addictive, natural complex pro-dopamine regulator (KB220), matching to one's neurotransmitter pathways associated reward gene polymorphisms, as previously proposed. Fried et al. (59) reported a case series about the novel treatment of screening with GARS and utilizing a customized pro-dopamine regulator matched to polymorphic reward genes with a hypodopaminergic risk. The proband was a female of 34 years with a history of cannabis abuse and alcoholism. She voluntarily entered treatment after experiencing a car accident while driving under the influence. Following an assessment, she was genotyped using the GARS and given a polymorphic matched neuro-nutrient with a KB220Z base. She successfully recovered from Substance Use Disorder (SUD) and experienced improved socialization, family, economic status, well-being, and attenuation of major depression. She tested urine negative over the first 2 months in treatment and a recent screening. Following ~2 months into the program, her parents also decided to take the GARS and

started taking the recommended variants. The proband's father (a binge drinker) and mother (no SUD) showed improvement in various behaviors. Finally, the proband's biological children were also GARS tested, showing a high risk for SUD. This three-generation case series represents an example of the impact of genetic information coupled with an appropriate DNA guided "Pro-Dopamine Regulator" to recover and enhance life.

Over the many years of the development of the putative pro-dopamine regulator, with the research ID code of KB220Z, there have been a plethora of studies showing remarkable benefits related to reward deficiency behaviors and associated drug and non-drug phenotypes (26, 27, 29, 51, 55, 56, 59, 60, 62–93).

This KB220Z variant has been the subject of at least 43 clinical and pre-clinical studies showing anti-RDS addictive behaviors via dopaminergic mechanisms [see Annotated Bibliography and review by Blum et al. (30)] and **Figure 2**.

Manza et al. (94) suggest that chronic cannabis abuse is associated with resting-state brain function changes, particularly





in dopaminergic nuclei implicated in psychosis, habit formation, and reward processing. Is it possible that by utilizing GARS-guided precision, KB220Z could help restore the normal functioning of reward processing and connectivity in cannabis-using subjects, especially in our youth and high-risk populations?

## ISSUES OF CANNABIS LEGALIZATION

Even though extensive research shows that chronic use of cannabis is associated with significant adverse health effects (16, 95–97), there is a disturbing trend of many states in the United States (US), and other countries legalize cannabis for unregulated recreational and medicinal use. Colorado was one of the first two U.S. states to legalize cannabis for recreational use for adults 21 and older. There are serious concerns regarding physical and mental health risks, particularly among adolescents who may use cannabis of high THC content. According to Parnes

et al. (98), two hypotheses have been studied. First, cannabis use among college students 21 years old and older would increase after recreational legalization. Second, there would be a positive correlation between the new cannabis legislation and out-of-state students' decision to attend a Colorado university as well as their cannabis use after that. However, the opposite was found. Data from a survey of 5,241 undergraduate students showed that cannabis use increased since recreational legalization for all students, particularly for those over 21 years. For past-month use frequency, no differences were found between pre-legalization and post-legalization (98).

Moreover, out-of-state students reported higher past 30-day use than in-state students. Indeed, one real concern relates to the post-legalization opening of retail cannabis stores and adult cannabis use throughout the country. Specifically, Everson et al. (99) evaluated this issue in Washington and found that frequent cannabis use grew significantly between 2009 and 2016 with greater access to cannabis retailers. Frequent use

increased among adults living within 0.8 miles of a retailer. Moreover, Klimer (100) developed a 14-point policy as follows: (1) Production, (2) Profit motive, (3) Power to regulate, (4) Promotion, (5) Prevention and treatment, (6) Policing and enforcement, (7) Penalties, (8) Prior criminal records, (9) Product types, (10) Potency, (11) Purity, (12) Price, (13) Preferences for licenses, and (14) Permanency. A crucial aspect of moving forward in terms of legalization must address the high content of THC in waxes and other products, as well as statewide inconsistencies (101).

On the other hand, the American Society of Addiction Medicine (ASAM) issued a policy statement (102) on marijuana and cannabinoids, recommending *decriminalization* instead of legalization of cannabis and cannabinoids. Furthermore, the legalization of the commercial sale and promotion of cannabis with high THC content for recreational use in many states (Alaska, California, Colorado, Illinois, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington) may lead to significant increases in THC intoxication, dependence, and addiction because of the euphoria. Consequently, the neurochemical impact on reward systems in the brain that can lead to neurological reward system deficits may also be significant and of great concern to clinicians.

Thus, until an FDA-approved therapy for treating cannabis use disorder and any of its adverse health components, developing a safe and responsible strategy toward decriminalizing cannabis and cannabis products seems paramount in the United States. As such, consideration of using KB220Z, a dopamine up-regulator discussed above, for restoring balanced neurotransmission and alleviating hypodopaminergia and its consequences like anhedonia (depression), cognitive decline, and other mental health effects due to chronic cannabis use. Similarly, the supplement N-acetylcysteine (NAC) to treat substance use disorders, including CUD, could be useful. In a double-blind, randomized control trial of a cohort of cannabis-dependent adolescents, Gray et al. (103) demonstrated that NAC is an effective treatment for cannabis use disorder, and Tomko et al. (104) revived NAC as a potential treatment for substance use disorders, including cannabis.

## CONCLUSION

Although the prevalence of recreational cannabis users at high risk for developing anhedonia and depression is unknown,

the amount of cannabis used (dose of THC) seems to be an important factor. Chronic use of high THC content cannabis, either by oral ingestion or vaping, results in reversible neuroanatomic alterations in the mesolimbic and cortical brain regions with subsequent hypodopaminergia and associated depression/anhedonia. Cannabis use among young adults causes these neuroanatomical and psychological changes, magnified by DNA polymorphisms in pro-dopamine reward genes (like DAT1, DRD2, DRD4, COMT). These DNA polymorphisms can be measured either before cannabis use (prophylaxis) or post-use (epigenetic). Treatment should involve the induction of dopamine homeostasis via pro-dopamine regulation and thereby ameliorate anhedonia. No FDA-approved therapies are currently available to treat CUD or any comorbidities, such as depression or cognitive decline (23, 58, 71, 94, 105–112). Using a dopamine up-regulator such as KB220Z to restore brain dopamine in hypodopaminergia until an FDA-approved therapy is available could be considered for chronic cannabis users with CUD. The development of an appropriate policy regarding the legalization of cannabis and cannabis products and decriminalization is needed.

## AUTHOR CONTRIBUTIONS

AB developed the schematic. The original manuscript was developed by KB and JK, and all authors commented and equally contributed.

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**Conflict of Interest:** KB is the inventor and patent holder of both GARS and Pro-dopamine regulators. He has licensed same to Ivtitalize Inc. KB owns stock in Ivtitalize Inc. LL is a paid consultant from Geneus Health, LLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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