



## ORIGINAL ARTICLE

## The Detrimental Effects of Cannabis on Brain. A Concise Review

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### Abstract

Marijuana and hashish, from the plant *Cannabis sativa* L, are the illicit drugs most frequently used worldwide. Cannabis is well known for its recreational effects being popular among adolescents and young adults and is often perceived as harmless. Cannabis, however, impairs working and short-term memory and is associated with decline in academic functioning, impaired driving skills, cognitive impairment, and progression to other illicit substance use. Cannabis use has also been linked to a propensity for developing psychotic events while neuroimaging studies indicated brain volume changes in heavy and chronic users. Cannabis effects are ascribed to its major psychoactive constituent delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) acting on at least two types of cannabinoid receptors. The effects of cannabis on brain are influenced by the age of initiating usage, frequency and potency of the cannabis preparation ( $\Delta^9$ -THC) as well as the ratio of  $\Delta^9$ -THC to the major non-psychoactive cannabinoid. The latter is thought to antagonize some of the adverse effects of  $\Delta^9$ -THC. The aim of this review is to summarize the evidence pertaining to the delirious effects of cannabis and its main psychoactive ingredient  $\Delta^9$ -THC on the brain.

### Key words

$\Delta^9$ -tetrahydrocannabinol; Brain; Cannabis; Cognition; Memory

### Introduction

Cannabis preparations from the plant *Cannabis sativa* L (family *Cannabaceae*) are the most widely used illicit substances worldwide. These are marijuana prepared from the dried flowering tops and leaves and hashish from the resin secreted by the female plant [1]. The use of cannabis is on the rise. It has been estimated in 2018 about 192 million adults globally have used cannabis as compared with 188 million in 2017. The

increase in the prevalence of cannabis use in the United States is attributed to the changes in legislation in some states, thereby, increasing the extent of exposure of the adult and youth populations to cannabis [2,3]. Cannabis use is particularly common among adolescents and high-school students, for it is estimated that globally 5.6% of students have used cannabis in 2017 [4]. In the United States, among persons aged  $\geq 12$  years 7.5% (19.8 million) have used marijuana in the preceding month [5]. UK data in 2012/13 estimates that 30.9% of those aged 16-24 years have ever used cannabis and that 13.5% have smoked cannabis in the preceding year [6]. Figures from European Union members, Norway and Turkey indicate that  $\sim 25\%$  of those aged 15-24 years are life-time users and that  $\sim 15\%$  have used cannabis in the past year [4]. Marijuana and hashish, are the illicit drugs most frequently used by school and University students in different countries eg, Egypt, Canada, Ireland [7-9].

Cannabis produces a sense of mild euphoria, relaxation, anxiety, difficulty in concentrating, loss of reality, altered body perception and change in body image, disconnected thoughts, intensification of sensory experiences, and distortion of time perception [10-13]. These effects are mediated by its major psychoactive constituent delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC) [14] acting on at least two types of G-protein-coupled cannabinoid (CB) receptors, with the CB1 receptor being expressed in high density on neuronal terminals in areas associated with cognition, memory, learning, emotions, appetite, and motor coordination such as the cerebral cortex, limbic system, amygdale, hippocampus, basal ganglia and cerebellum. The second receptor, CB2, is found principally in the periphery, mostly in blood cells

with immune functions [15].  $\Delta^9$ -THC acts as partial agonist at CB1 and CB2 receptors [16]. Endogenous ligands (endocannabinoids) are also present eg., anandamide, 2-arachidonylglycerol, noladine ether, and virodhamine and together with the cannabinoid receptors, their lipid precursors, inactivating enzymes, and their molecular targets constitute the endocannabinoid system [15,17]. Besides  $\Delta^9$ -THC, the cannabis plant contains more than 120 cannabinoids, most of them are not psychoactive and exist in very small amounts. Examples of non-psychoactive terpenophenolic cannabinoids or phytocannabinoids are cannabidiol, cannabigerol, cannabidivarin and  $\Delta^9$ -tetrahydrocannabivarin [18-20]. Pharmacological studies indicated that these cannabinoids have additive, synergistic or even antagonistic effects with  $\Delta^9$ -THC and thus may modulate its actions when herbal cannabis is smoked [16,21]. Some cannabinoids eg., cannabidiol (CBD), cannabigerol, and cannabidivarin have shown therapeutic potential in preclinical models of inflammatory bowel disease [22] and epilepsy [23,24]. Moreover, cannabis extracts with rich cannabidiol contents were reported to be of benefit in refractory epilepsies [25]. Cannabis also contains ~650 other compounds including terpenoids, flavonoids, sterols, alkanes, and other chemicals [19,20]. However, the oral administration of  $\Delta^9$ -THC (20 mg, q.i.d.) to healthy volunteers produced similar effects to that of smoked marijuana (3.1%  $\Delta^9$ -THC, q.i.d.) i.e., "high" and increased food intake [26]. The effects perceived after smoking cannabis are therefore caused by  $\Delta^9$ -THC.

The widespread use of marijuana and hashish among adolescents is because these psychoactive products are often perceived as harmless or innocent [27]. Besides, they are easy to obtain and cheaper than other illicit substances [28]. Mokrysz et al. [29] compared the acute effects of vaporized cannabis in adolescent differ from that in adult male cannabis users. Participants received 0.89 mg/kg of cannabis (~ 8.0 mg  $\Delta^9$ -THC). Compared to adults, adolescents felt less stoned after cannabis, felt the drug effect less, were not satiated by cannabis, and exhibited impaired inhibitory processes. They also reported fewer psychotomimetic effects and less memory problems than adults. These findings may explain the frequency and continued use of cannabis by adolescents. Cannabis use, however, is not without harm. Cannabis has been associated with decline in academic functioning and achievement, impaired driving skills, cognitive impairment [30,31], progression to other illicit substance use [32] and propensity for developing psychosis [33]. Moreover, neuroimaging studies showed that heavy and chronic cannabis is associated with structural brain changes [34,35]. These effects of cannabis are expected to be triggered when cannabis is started during adolescence [36]. Cannabis on the average contains between 2.1% and 3.5%  $\Delta^9$ -THC in the flowering tops, upper leaves and resin of the female plant [37,38]. Levels of  $\Delta^9$ -THC, however,

showed dramatic increase over the past decade, from ~ 3% to 12-16% or even higher [39-41]. Moreover, with changes in cannabis policy and legalization of medical or recreational cannabis, it is expected that adolescent use will increase with consequent rise in health problems [42].

### Cannabis Associated Psychosis

Schizophrenia is a devastating mental disorder that affects 1% of the population worldwide [43]. Symptoms fall into (i) psychotic or positive symptoms eg., hallucinations, delusions, and thought disorder; (ii) deficit or negative symptoms eg., social withdrawal, lack of motivation and expression of affect, inability to experience pleasure, and impairment of spontaneous speech, and (iii) cognitive impairment [44]. These symptoms are caused by an increase in subcortical release of dopamine and decreased activation of D1 receptors in the prefrontal cortex [45]. Schizophrenic symptoms were also reproduced in healthy humans by the administration of sub-anesthetic doses of ketamine, a non competitive antagonist of the glutamatergic *N*-methyl-*D*-aspartate (NMDA) receptor, thereby implicating role for NMDA receptor in path physiology of schizophrenia [46].

Increasingly available evidence suggests that heavy and persistent use of cannabis is linked to the development of psychotic events and/or schizophrenia in those with genetic predisposition. This is especially so if use was initiated at a relatively young age [47]. Cannabis is the most frequently abused illicit substance among patients with schizophrenia [48] with lifetime use and misuse prevalence estimates of 42% and 23%, respectively [49]. Use of cannabis was associated with both negative and positive features of schizophrenia [50]. A survey of the self perceived effects of cannabis showed that 40% of subjects who were cannabis users in their adolescence and may still be users, experienced paranoid feelings (suspiciousness) and delusions, while 7% had hallucinations when using cannabis [12]. A study in heavy and chronic users of only cannabis reported the occurrence of hallucinations (auditory 39.6, visual in 21.1%) while 54.2% of the abusers experienced delusions mostly in the form of ideas of reference and persecution. Elevated cannabinoids levels in head hair samples were found in those with auditory hallucinations compared to users with no hallucinations [51].

Schizophrenic symptoms can be reproduced if the main psychoactive ingredient of cannabis is injected into man. Subjective feelings of depersonalization, disconnected thoughts and paranoid ideas were reported by normal volunteers after oral administration of  $\Delta^9$ -THC (0.5 mg/kg) but not cannabidiol (1 mg/kg) [13]. Also, the intravenous injection of  $\Delta^9$ -THC (2.5 and 5 mg) to healthy cannabis users resulted in transient positive (eg., suspiciousness, paranoid and grandiose delusions) and negative symptoms (eg., psychomotor retardation,

and emotional withdrawal) of schizophrenia [10]. In addition, in subjects with paranoid ideation,  $\Delta^9$ -THC (1.5 mg, i.v.) was found to significantly increase paranoia.  $\Delta^9$ -THC also led to the development of worry, anxiety depression, and negative thoughts about the self [52]. Psychotic symptoms eg., depersonalization, paranoid feelings, derealization and irrational anxiety were also induced in healthy subjects who are recent users of cannabis following oral intake of  $\Delta^9$ -THC decoction (16.5 mg) or synthetic  $\Delta^9$ -THC (dronabinol, 20 mg/kg). The  $\Delta^9$ -THC and 11-OH-THC blood levels reached a concentration of 1.8 and 5.2 ng/mL after dronabinol and 6.2 and 3.9 ng/mL following the hemp milk decoction [53]. In healthy subjects who were cannabis users, psychotic symptoms and levels of anxiety increased following ingestion of 10 mg  $\Delta^9$ -THC but not cannabidiol. This effect of  $\Delta^9$ -THC was associated with activation of ventrostriatal activity [54]. Other studies suggested that cannabidiol could attenuate or prevent the occurrence of psychotic symptoms that followed  $\Delta^9$ -THC administration [55,56]. In healthy volunteers, psychotic symptoms induced by  $\Delta^9$ -THC (1.25 mg, i.v.) were diminished by prior administration of cannabidiol (5 mg, i.v.) [55]. In another study, healthy subjects who receive oral cannabidiol (600 mg) prior to  $\Delta^9$ -THC (1.5 mg, i.v.) were less likely to develop positive psychotic symptoms and paranoia as compared to the placebo group [56]. It is therefore conceivable that cannabis with high cannabidiol content are probably associated with much lower risk for causing psychotic events as compared to cannabis rich in  $\Delta^9$ -THC. This is however, is not always the case. In their study, Morgan et al. investigated the acute effects of  $\Delta^9$ -THC (8 mg), CBD (16 mg) or their combination (8 mg  $\Delta^9$ -THC + 16 mg CBD) in users of cannabis. The cannabinoids were given by inhalation through a vaporizer. They found an increase in negative symptoms besides perceptual distortions and cognitive disorganisation which occurred after  $\Delta^9$ -THC alone or both  $\Delta^9$ -THC/CBD. The concurrent administration of CBD with  $\Delta^9$ -THC in a 2:1 ratio did not attenuate the acute psychotic symptoms induced by vaporized  $\Delta^9$ -THC [57].

Studies showed that starting cannabis in adolescence results in 2-3 fold increments in the risk for developing schizophrenia late in life [58]. The younger the age of cannabis initiation, the more frequent use and the potency of cannabis were all risk factors associated with earlier onset of psychosis. Thus, initiating cannabis usage at age 15 or younger was associated with an earlier onset of psychosis compared starting cannabis at a later age. Moreover, progression to high levels of daily pre-onset cannabis use rather than the frequency of use was associated with increasing the relative risk of onset of psychosis more in females than in males [59]. Subjects presenting with a first episode of psychosis were reported to have used high-potency cannabis (sinsemilla, 'skunk') for longer (> than 5 years)

and with higher frequency (daily users) compared with their control group. The sinsemilla variety of cannabis contains on the average 12-18%  $\Delta^9$ -THC and < than 1.5% cannabidiol (CBD) [60]. Di Forte et al. [61] reported that daily use of high-potency cannabis was also associated with an earlier onset of psychosis. Studies also suggested a link between the genetic risk for developing schizophrenia and excessive usage of cannabis use during adolescence (16-20 years) [47]. This effect of cannabis in the adolescent brain could be the result of persistent activation of CB1 receptors by  $\Delta^9$ -THC and consequent disturbance of neuronal migration, axonal pathfinding and synaptogenesis controlled by the endogenous cannabinoid system [62]. Epstein et al. [63] found an atypical pattern of maturation in heteromodal association cortex, an area linked to cognitive development, in adolescents with cannabis use disorder relative to non-users. Cerebellar white-matter volume is decreased in cannabis users with and without schizophrenia [64]. Moreover, compared with non-users of cannabis, brain volume changes eg., greater regional grey matter reduction in the cerebellum have been detected in young cannabis users diagnosed with first-episode schizophrenia [65] (Table 1 and Table 2).

### Cannabis and Cognitive Impairment

One of the mostly reported adverse effects of cannabis use is its ability to impair short-term and working memory [66]. Short-term is a capacity-limited and transient form of memory that supports the temporary storage and maintenance of internal representations [67]. Working memory maintains limited information temporary available for immediate access by other cognitive processes. It is important for such tasks a language comprehension, planning, problem-solving, and reasoning [68]. The effect of cannabis on memory has been demonstrated after acute or chronic use in humans [66,69,70] and experimental animals [71,72]. In humans, cannabis impaired immediate and delayed free recall of information, verbal fluency [10], verbal memory (prose recall) [73], working memory [10,73], semantic processing and retrieval performance [74], and prospective memory [75]. Initiation of cannabis use at an earlier age was associated with worse verbal memory performance [76]. A study involving undergraduates studying at universities revealed impairment during the video-based prospective memory task in cannabis users compared with non-users [75]. Frequent cannabis users displayed altered neurophysiological dynamics in the left superior parietal cortex during working memory processing [77].

Studies showed that cognitive functions deteriorate with increasing years of heavy and frequent use of cannabis with long-term users displaying worse performance on verbal memory and psychomotor speed [78]. Persistent cannabis use, assessed over 20 years was associated with decline in neuropsychological

**Table 1:** Effects of cannabis in humans

Acute effects	Delayed effects in frequent heavy users
• Mild euphoria	• IQ decline
• Relaxation	• Decline in academic functioning and achievement
• Difficulty in concentrating	• Cognitive impairment
• Anxiety	• Cannabis dependence syndrome
• Intensification of sensory experiences	• Propensity for developing schizophrenia
• Distortion of time perception	• Increase in likelihood for using other illicit drugs
• Disconnected thoughts	
• Loss of reality	
• Altered body perception	
• Change in body image	
• Psychotic symptoms <ul style="list-style-type: none"> <li>• Depersonalization</li> <li>• Serialization</li> <li>• Suspiciousness</li> <li>• Paranoid feelings</li> </ul>	
• Memory impairments involving: <ul style="list-style-type: none"> <li>• Immediate and delayed free recall of information</li> <li>• Working memory</li> <li>• Verbal memory</li> <li>• Prospective memory</li> <li>• Semantic processing and retrieval performance</li> </ul>	
• Impaired motor coordination	
• Impaired driving skills	
• Increased food intake	

**Table 2:** Schizophrenic symptoms after  $\Delta^9$ -THC administration in humans

Subjects	THC dose	Schizophrenic symptoms	Study
Normal volunteers	$\Delta^9$ -THC (0.5 mg/kg, orally)	Depersonalization, disconnected thoughts, paranoid ideas.	[13]
Healthy cannabis users	$\Delta^9$ -THC (2.5, and 5 mg, i.v.)	Positive symptoms: Suspiciousness, paranoid and grandiose delusions. Negative symptoms: Psychomotor retardation, and emotional withdrawal.	[10]
Subjects with paranoid ideation	$\Delta^9$ -THC (1.5 mg, i.v.)	↑ Paranoia Worry, anxiety, depression, and negative thoughts about the self.	[51]
Healthy subjects who were recent users of cannabis	$\Delta^9$ -THC milk decoction (16.5 mg) or synthetic $\Delta^9$ -THC (dronabinol; 20 mg/kg) orally.	Depersonalization, paranoid feelings, derealization and irrational anxiety.	[52]
Healthy subjects who were cannabis users	$\Delta^9$ -THC (10 mg, orally)	↑ Psychotic symptoms ↑ Levels of anxiety	[53].
Cannabis users	$\Delta^9$ -THC 8 mg or $\Delta^9$ -THC 8 mg + CBD 16 mg (by inhalation through a vaporizer).	↑ BPRS negative symptoms ↑ Perceptual distortions and cognitive disorganization	[57]

functioning; executive functioning, processing speed, working memory, perceptual reasoning, and verbal comprehension. More persistent adolescent-onset cannabis users showed greater IQ decline from childhood

to adulthood [79]. Younger age of cannabis use disorder onset, regular and maximum daily use of cannabis was associated with lower academic achievement [80]. The decline in cognitive functioning seems to

persist for sometime after cessation of cannabis use, thereby, suggesting a neurotoxic effect of cannabis on the adolescent brain [79], the critical period for neural maturation [81,82]. The cannabis-induced impairment in memory is mediated by its major psychoactive constituent  $\Delta^9$ -THC-induced activation of cannabinoid CB1 receptor in brain. Brain activation assessed using a pictorial memory task in healthy volunteers showed that  $\Delta^9$ -THC inhalation caused reductions in activity during encoding in the right insula, the right inferior frontal gyrus, and the left middle occipital gyrus [83]. In healthy volunteers, acute intravenous administration of 2.5 and 5 mg  $\Delta^9$ -THC resulted in impaired immediate and delayed word recall, verbal fluency and working memory [10]. In addition, ingestion of  $\Delta^9$ -THC was able to modulate mediotemporal cortex function during verbal paired associate learning which might account for the effects of cannabis on verbal learning [54]. Cannabis given at single dose of 300  $\mu$ g/kg by inhalation through a vaporizer to healthy, occasional cannabis users, was found to increase immediate false-memories [84]. Impaired verbal and working memory was also reported in cannabis users after Bedrobinol at a dose of 66.67 mg (containing 16.1%  $\Delta^9$ -THC and <1% CBD) administered as 'joints' [71].

Curran et al. [85] investigated the acute effects of  $\Delta^9$ -THC in infrequent cannabis users and found that oral  $\Delta^9$ -THC (15 mg and 7.5 mg) impaired episodic memory and learning in a dose-dependent manner. Whether the non-psychotropic cannabidiol antagonizes the memory impairing action of  $\Delta^9$ -THC has been investigated. Arkell et al. [86] assessed simulated driving and cognitive performance of healthy volunteers with a history of light cannabis use, following vaporization of 125 mg of  $\Delta^9$ -THC -dominant and THC/CBD equivalent cannabis. Vaporization of either type of cannabis impaired driving during a car-following task, reduced confidence in driving and caused acute cognitive impairment. Significantly

higher peak plasma  $\Delta^9$ -THC levels occurred after  $\Delta^9$ -THC/CBD cannabis compared with  $\Delta^9$ -THC-dominant variety. Another study in cannabis users reported impaired working and episodic memory by vaporized  $\Delta^9$ -THC (8 mg) alone or  $\Delta^9$ -THC 8 mg/CBD 16 mg [57]. Other researchers studied the acute effects of cannabis of varying  $\Delta^9$ -THC: CBD ratios on memory in a verbal recognition task in regular cannabis users. Subjects consuming primarily  $\Delta^9$ -THC -based strains performed worse memory accuracy after use that correlated with blood  $\Delta^9$ -THC levels. In contrast, consuming the combination of CBD and  $\Delta^9$ -THC was not associated with impaired memory [87].

Animal studies demonstrated impaired memory performance after the administration of hashish/marijuana extracts or  $\Delta^9$ -THC. In adolescent rhesus monkeys  $\Delta^9$ -THC (30-240  $\mu$ g/kg, iv.) induced spatial working memory deficits [88]. Hashish extract containing 38.6-39.4%  $\Delta^9$ -THC and 47.7-48.5% cannabidiol administered orally to mice before learning was found to interfere with memory processing. The doses given corresponded to 1, 5, and 10 mg  $\Delta^9$ -THC/kg [89]. In mice,  $\Delta^9$ -THC (3.0 mg/kg) disrupted performance of the working memory version of the Morris water maze test; the effect being reversed by the selective CB1 receptor antagonist SR 141716A [90]. Other researchers reported longer escape latencies in the Morris water maze test in mice 3 weeks after a single injection of a small dose of  $\Delta^9$ -THC (0.001 mg/kg THC) [91]. Mice fed with a diet supplemented with THC for 6 weeks displayed impaired spatial memory in the Morris water maze [92]. The effect of cannabis extract rich in  $\Delta^9$ -THC was investigated in mice. Cannabis was subcutaneously given at doses of 5, 10 or 20 mg/kg (expressed as  $\Delta^9$ -THC) daily for 30 days. Cannabis significantly increased latencies to escape to hidden plate. It also increased memory impairment caused by the anti-cholinergic agent scopolamine [73]. The impairment of spatial memory caused by  $\Delta^9$ -THC is

**Table 3:** Memory impairments after  $\Delta^9$ -THC administration in humans

Subjects	THC dose	Memory impairment	Study
Healthy volunteers	$\Delta^9$ -THC (2.5 and 5 mg, i.v.)	Impaired immediate and delayed word recall, verbal fluency and working memory.	[10]
Infrequent cannabis users	$\Delta^9$ -THC (15 mg and 7.5 mg, orally)	Impaired episodic memory and learning (dose-dependent).	[82]
Healthy volunteers, with a history of light cannabis use	$\Delta^9$ -THC –dominant cannabis (125 mg by vaporization)	Impaired driving during a car-following task ↓ Confidence in driving Acute cognitive impairment.	[83]
Healthy, occasional cannabis users	$\Delta^9$ -THC (300 $\mu$ g/kg, single dose by vaporization)	↑ Immediate false-memories	[84]
Healthy, nondependent but experienced, cannabis users	66.67 mg Bedrobinol (16.1% THC and <1% CBD) using 'joints',	Impaired verbal and working memory.	[71]
Cannabis users	$\Delta^9$ -THC 8 mg or $\Delta^9$ -THC 8 mg + CBD 16 mg (by inhalation through a vaporizer).	Impaired episodic and working memory	[57]

mediated through cannabinoid CB1 receptors since it was reversed by cannabinoid CB1 receptor antagonist [93]. In contrast to  $\Delta^9$ -THC, CBD-rich extracts [72] or diet supplemented with CBD [92] had no effect on spatial memory. These results support human studies suggesting that CBD does not affect cognition in healthy individuals and can even antagonize memory impairment by  $\Delta^9$ -THC [94,95] (Table 3).

### Changes in Brain Structure in Users of Cannabis

Cannabis has been shown to be associated with changes in brain structure, particularly among those who started using cannabis at an early age. Filbey et al. [96] have found significantly decreased bilateral orbitofrontal gyri volume in marijuana users compared with controls. Battistella et al. [34] reported reductions of medial temporal cortex, temporal pole, parahippocampal gyrus, insula, and orbitofrontal cortex in regular marijuana users compared with occasional users. In addition, compared with non-users, frequent users of cannabis showed a decrease in cortical thickness of the entorhinal cortex which correlated with age of first use and memory performance [76]. Yücel et al. [35] found that in contrast to users of cannabis containing cannabidiol, subjects who have used cannabis containing only  $\Delta^9$ -THC for an average of 15.4 years exhibited hippocampal volume reduction that was restored after prolonged abstinence. This suggests that cannabidiol, a major non-psychoactive cannabinoid might be antagonizing the neurotoxic action of  $\Delta^9$ -THC. Another study by Burggren et al. [97] has shown that the effects of chronic adolescent use of cannabis on hippocampal cortical loss are maintained into late life and thus could exacerbate age-related cognitive decline. Other researchers found greater gray matter volume in different brain regions including bilateral medial temporal lobes and cerebellum in 14-year adolescents who have used cannabis only once or twice [98].

### Concluding Remarks

It is clear that there is increasingly available evidence which strongly support a detrimental effect for  $\Delta^9$ -THC-rich cannabis on brain cognitive functioning and structure. This is especially so during adolescence, the critical period for brain maturation. These effects of cannabis are related to the age of initiation, type and consequently the content of  $\Delta^9$ -THC and the duration of exposure. The mechanisms underlying the neurotoxic effects of  $\Delta^9$ -THC are to be delineated.

### Declarations

#### Author contributions

OMEAS contributed solely to the manuscript.

#### Conflicts of interest

The author declare that he has no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

### Consent of publication

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### References

1. Market analysis of plant-based drugs-Opiates, cocaine, cannabis (2017) United Nations Office on Drugs and Crime, World Drug Report, United Nations publication, Sales No. E.17.XI.9, Vienna, Austria: 37-45.
2. World Drug Report 2019 (United Nations publication, Sales No. E.19.XI.8).
3. World Drug Report 2020 (United Nations publication, Sales No. E.20.XI.6).
4. World Drug Report 2018 (United Nations publication, Sales No. E.18.XI.9).
5. Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, et al. (2016) National Estimates of Marijuana Use and Related Indicators – National Survey on Drug Use and Health, United States, 2002-2014. *MMWR Surveill Summ* 65: 1-25.
6. Home Office Statistics. Drug Misuse: Findings from the 2012/13 Crime Survey for England and Wales. Kew, UK: National Archives; July 2013.
7. Abdel-Salam OME, Galal AF, Elshebiny SA, Gaafar AEDM (2017) International Aspects of Cannabis Use and Misuse: Egypt. In: *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis, and Treatment*, 1<sup>st</sup> Edition. Preedy V (ed). Academic Press, Elsevier Science Publishing Co Inc: 505-516.
8. Leos-Toro C, Rynard V, Murnaghan D, MacDonald JA, Hammond D (2019) Trends in cannabis use over time among Canadian youth: 2004-2014. *Prev Med* 118: 30-37.
9. Skinner R, Conlon L, Gibbons D, McDonald C (2011) Cannabis use and non-clinical dimensions of psychosis in university students presenting to primary care. *Acta Psychiatr Scand* 123: 21-27.
10. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, et al. (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 29: 1558-1572.
11. Hall W, Degenhardt L (2009) Adverse health effects of non-medical cannabis use. *Lancet* 374: 1383-1391.
12. Camera AA, Tomaselli V, Fleming J, Jabbar GA, Trachtenberg M, et al. (2012) Correlates to the variable effects of cannabis in young adults: a preliminary study. *Harm Reduct J* 9: 15.
13. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG (1982) Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* 76: 24.

14. Mechoulam R, Gaoni Y (1967) The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. *Tetrahedron Lett* 12: 1109-1111.
15. Svíženská I, Dubový P, Šulcová A (2008) Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures —A short review. *Pharmacol Biochem Behav* 90: 501-511.
16. Pertwee RG (2008) The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids:  $\Delta^9$ -tetrahydrocannabinol, cannabidiol and  $\Delta^9$ -tetrahydrocannabivarin. *Br J Pharmacol* 153: 199-215.
17. Mechoulam R, Parker LA (2013) The endocannabinoid system and the brain. *Annu Rev Psychol* 64: 21-47.
18. ElShohly MA. Chemical constituents of cannabis (2002) In: Grotenhermen F, Russo E (eds). *Cannabis and cannabinoids. Pharmacology, toxicology and therapeutic potential*. New York: Haworth Press Inc: 27-36.
19. Brenneisen R (2006) Chemistry and analysis of phytocannabinoids and other cannabis constituents. In: ElShohly MA (ed) *Forensic science and medicine: marijuana and the cannabinoids*. Humana, Totowa: 17-49.
20. Radwan MM, ElShohly MA, El-Alfy AT, Ahmed SA, Slade D, et al. (2015) Isolation and Pharmacological evaluation of minor cannabinoids from high-potency *Cannabis sativa*. *J Nat Prod* 78: 1271-1276.
21. Pertwee RG, Thomas A, Stevenson LA, Ross RA, Varvel SA, et al. (2007) The psychoactive plant cannabinoid,  $\Delta^9$ -tetrahydrocannabinol, is antagonized by  $\Delta^8$ - and  $\Delta^9$ -tetrahydrocannabivarin in mice *in vivo*. *Br J Pharmacol* 150: 586-594.
22. Borrelli F, Fasolino I, Romano B, Capasso R, Maiello F, et al. (2013) Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochem Pharmacol* 85: 1306-1316.
23. Amada N, Yamasaki Y, Williams CM, Whalley BJ (2013) Cannabidiol (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression. *Peer J* 1: e214.
24. Do Val-da Silva RA, Peixoto-Santos JE, Kandravicius L, De Ross JB, Esteves I, et al. (2017) Protective effects of cannabidiol against seizures and neuronal death in a rat model of mesial temporal lobe epilepsy. *Front Pharmacol* 8: 131.
25. Press CA, Knupp KG, Chapman KE (2015) Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav* 45: 49-52.
26. Hart CL, Ward AS, Haney M, Comer SD, Foltin RW, et al. (2002) Comparison of smoked marijuana and oral Delta(9)-tetrahydrocannabinol in humans. *Psychopharmacology (Berl)* 164: 407-415.
27. Hasin DS (2018) US Epidemiology of cannabis use and associated problems. *Neuropsychopharmacology* 43: 195-212.
28. Abdel-Salam OME (2019) The harm of cannabis in adolescents. *Biomed Pharmacol J* 12: 495-498.
29. Mokrysz C, Freeman TP, Korkki S, Griffiths K, Curran HV (2016) Are adolescents more vulnerable to the harmful effects of cannabis than adults? A placebo-controlled study in human males. *Transl Psychiatry* 6: e961.
30. Hall W (2015) What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* 110: 19-35.
31. Stiby AI, Hickman M, Munafò MR, Heron J, Yip VL, et al. (2015) Adolescent cannabis and tobacco use and educational outcomes at age 16: birth cohort study. *Addiction* 110: 658-668.
32. Swift W, Coffey C, Degenhardt L, Carlin JB, Romaniuk H, et al. (2012) Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. *J Epidemiol Community Health* 66: e26.
33. Andréasson S, Engstrom A, Allebeck P, Rydberg U (1987) Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet* 2: 1483-1486.
34. Battistella G, Fornari E, Annoni JM, Chtioui H, Dao K, et al. (2014) Long-term effects of cannabis on brain structure. *Neuropsychopharmacology* 39: 2041-2048.
35. Yücel M, Lorenzetti V, Suo C, Zalesky A, Fornito A, et al. (2016) Hippocampal harms, protection and recovery following regular cannabis use. *Transl Psychiatry* 6: e710.
36. Hall WD (2006) Cannabis use and the mental health of young people. *Aust N Z J Psychiatry* 40: 105-113.
37. Ashton CH (2001) Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry* 178: 101-106.
38. Potter DJ, Clark P, Brown MB (2008) Potency of  $\Delta^9$ -THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *J Forensic Sci* 53: 90-94.
39. Radwan MM, Elshohly MA, Slade D, Ahmed SA, Wilson L, et al. (2008) Non-cannabinoid constituents from a high potency *Cannabis sativa* variety. *Phytochemistry* 69: 2627-2633.
40. Swift W, Wong A, Li KM, Arnold JC, McGregor IS (2013) Analysis of cannabis seizures in NSW, Australia: Cannabis potency and cannabinoid profile. *PLoS ONE* 8: e70052.
41. Souleman AMA, Gaafar AE-DM, Abdel-Salam OM, ElShebiny SA (2017) Determination of delta-9-tetrahydrocannabinol content of cannabis seizures in Egypt. *Asian Pac J Trop Med* 10: 311-314.
42. Blevins CE, Marsh E, Banes KE, Stephens RS, Walker DD, et al. (2018) The implications of cannabis policy changes in Washington on adolescent perception of risk, norms, attitudes, and substance use. *Subst Abuse* 12: 117822181881549.
43. The American Psychiatric Publishing textbook of schizophrenia (2006) Lieberman JA, Stroup TS, Perkins DO (eds), 1st ed, 2006. American Psychiatric Publishing, Inc. Washington, DC London, England.
44. Wong AHC, Van Tol HHM (2003) Schizophrenia: from phenomenology to neurobiology. *Neurosci Biobehav Rev* 27: 269-306.
45. Brisch R, Saniotis A, Wolf R, Biellau H, Bernstein HG, et al. (2014) The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. *Front Psychiatry* 5: 47.
46. Mechri A, Saoud M, Khiari G, d'Amato T, Dalery J, et al. (2001) Glutaminergic hypothesis of schizophrenia: clinical research studies with ketamine. *Encephale* 27: 53-59.
47. Hiemstra M, Nelemans SA, Branje S, van Eijk KR, Hottenga JJ, et al. (2018) Genetic vulnerability to schizophrenia is associated with cannabis use patterns during adolescence. *Drug Alcohol Depend* 190: 143-150.
48. Bersani G, Orlandi V, Kotzalidis GD, Pancheri P (2002)

- Cannabis and schizophrenia: impact on onset, course, psychopathology, and outcomes. *Eur Arch Psychiatry Clin Neurosci* 252: 86-92.
49. Green B, Young R, Kavanagh D (2005) Cannabis use and misuse prevalence among people with psychosis. *Br J Psychiatry* 187: 306-313.
50. Stefanis NC, Delespaul P, Henquet C, Bakoula C, Stefanis CN, et al. (2004) Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction* 99: 1333-1341.
51. Nestoros JN, Vakonaki E, Tzatzarakis MN, Alegakis A, Skondras MD, et al. (2017) Long lasting effects of chronic heavy cannabis abuse. *Am J Addict* 26: 335-342.
52. Freeman D, Dunn G, Murray RM, Evans N, Lister R, et al. (2015) How cannabis causes paranoia: using the intravenous administration of  $\Delta^9$ -tetrahydrocannabinol (THC) to identify key cognitive mechanisms leading to paranoia. *Schizophr Bull* 41: 391-399.
53. Favrat B, Ménétrey A, Augsburg M, Rothuizen LE, Appenzeller M, et al. (2005) Two cases of "cannabis acute psychosis" following the administration of oral cannabis. *BMC Psychiatry* 5: 17.
54. Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, et al. (2009) Modulation of mediotemporal and ventrostriatal function in humans by  $\Delta^9$ -tetrahydrocannabinol. A neural basis for the effects of cannabis sativa on learning and psychosis. *Arch Gen Psychiatry* 66: 442-451.
55. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, et al. (2010) Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 35: 764-774.
56. Englund A, Morrison PD, Nottage J, Hague D, Kane F, et al. (2013) Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol* 27: 19-27.
57. Morgan CJA, Freeman TP, Hindocha C, Schafer G, Gardner C, et al. (2018) Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function. *Translational psychiatry* 8: 181.
58. Arseneault L, Cannon M, Witton J, Murray RM (2004) Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry* 184: 110-117.
59. Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, et al. (2009) Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. *Am J Psychiatry* 166: 1251-1257.
60. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, et al. (2009) High-potency cannabis and the risk of psychosis. *Br J Psychiatry* 195: 488-491.
61. Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, et al. (2014) Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin* 40: 1509-1517.
62. Lutz B (2009) From molecular neurodevelopment to psychiatry: new insights in mechanisms underlying Cannabis-induced psychosis and schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 259: 369-370.
63. Epstein KA, Kumra S (2015) Altered cortical maturation in adolescent cannabis users with and without schizophrenia. *Schizophr Res* 162: 143-152.
64. Solowij N, Yücel M, Respondek C, Whittle S, Lindsay E, et al. (2011) Cerebellar white-matter changes in cannabis users with and without schizophrenia. *Psychol Med* 41: 2349-2359.
65. Cohen M, Rasser PE, Peck G, Carr VJ, Ward PB, et al. (2012) Cerebellar grey-matter deficits, cannabis use and first-episode schizophrenia in adolescents and young adults. *Int J Neuropsychopharmacol* 15: 297-307.
66. Solowij N, Battisti R (2008) The chronic effects of cannabis on memory in humans: a review. *Curr Drug Abuse Rev* 1: 81-98.
67. Baddeley A (2001) The concept of episodic memory. *Philos Trans R Soc Lond B Biol Sci* 356: 1345-1350.
68. Awh E, Jonides J (2001) Overlapping mechanisms of attention and spatial working memory. *Trends Cogn Sci* 5: 119-126.
69. Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, et al. (2011) Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology (Berl)* 216: 131-44.
70. Ranganathan M, D'Souza DC (2006) The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology* 188: 425-444.
71. Hindocha C, Freeman TP, Xia JX, Shaban NDC, Curran HV (2017) Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: a placebo-controlled trial. *Psychol Med* 47: 2708-2719.
72. Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G (2004) Differential effects of THC or CBD-rich cannabis extracts on working memory in rats. *Neuropharmacology* 47: 1170-1179.
73. Abdel-Salam OME, Salem NA, El-Shamarka ME-S, Ahmed NA-S, Hussein JS, et al. (2013) Cannabis-induced impairment of learning and memory: Effect of different nootropic drugs. *EXCLI J* 12: 193-214.
74. Fletcher P, Honey G (2006) Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn Sci* 10: 167-174.
75. Bartholomew J, Holroyd S, Heffernan TM (2010) Does cannabis use affect prospective memory in young adults? *J Psychopharmacol* 24: 241-246.
76. Levar N, Francis AN, Smith MJ, Ho WC, Gilman JM (2018) Verbal memory performance and reduced cortical thickness of brain regions along the uncinata fasciculus in young adult cannabis users. *Cannabis Cannabinoid Res* 3: 56-65.
77. Jager G, Kahn RS, van den Brink W, van Ree JM, Ramsey NF (2006) Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. *Psychopharmacology* 185: 358-368.
78. Messinis L, Kyprianidou A, Malefaki S, Papathanasopoulos P (2006) Neuropsychological deficits in long-term frequent cannabis users. *Neurology* 66: 737-739.
79. Meier MH, Caspi A, Ambler A, Harrington HL, Houts R, et al. (2012) Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA* 109: E2657-E2664.
80. Hooper SR, Woolley D, De Bellis MD (2014) Intellectual, neurocognitive, and academic achievement in abstinent adolescents with cannabis use disorder. *Psychopharmacology (Berl)* 231: 1467-1477.



81. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, et al. (2002) Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA* 287: 1123-1131.
82. Crews F, He J, Hodge C (2007) Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav* 86: 189-199.
83. Bossong MG, Jager G, van Hell HH, Zuurman L, Jansma JM, et al. (2012) Effects of  $\Delta^9$ -Tetrahydrocannabinol administration on human encoding and recall memory function: A pharmacological fMRI study. *J Cogn Neurosci* 24: 588-599.
84. Kloft L, Otgaar H, Blokland A, Monds LA, Toennes SW, et al. (2020) Cannabis increases susceptibility to false memory. *Proc Natl Acad Sci U S A* 117: 4585-4589.
85. Curran HV, Brignell C, Fletcher S, Middleton P, Henry J (2002) Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl)* 164: 61-70.
86. Arkell TR, Lintzeris N, Kevin RC, Ramaekers JG, Vandrey R, et al. (2019) Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. *Psychopharmacology* 236: 2713-2724.
87. Curran T, Devillez H, York Williams SL, Bidwell LC (2020) Acute effects of naturalistic THC vs. CBD use on recognition memory: a preliminary study. *J Cannabis Res* 2: 28.
88. Verrico CD, Liu S, Bitler EJ, Gu H, Sampson AR, et al. (2012) Delay- and dose-dependent effects of  $\Delta^9$ -tetrahydrocannabinol administration on spatial and object working memory tasks in adolescent rhesus monkeys. *Neuropsychopharmacology* 37: 1357-1366.
89. Frischknecht HR, Siegfried B, Schiller M, Waser PG (1985) Hashish extract impairs retention of defeat-induced submissive behavior in mice. *Psychopharmacology (Berl)* 86: 270-273.
90. Varvel S, Hamm R, Martin B, Lichtman A (2001) Differential effects of  $\Delta^9$ -THC on spatial reference and working memory in mice. *Psychopharmacology* 157: 142-150.
91. Tselnicker I, Keren O, Hefetz A, Pick CG, Sarne Y (2007) A single low dose of tetrahydrocannabinol induces long-term cognitive deficits. *Neurosci Lett* 411: 108-111.
92. Wolf SA, Bick-Sander A, Fabel K, Leal-Galicia P, Tauber S, et al. (2010) Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis. *Cell Commun Signal* 8: 12.
93. Egashira N, Manome N, Mishima K, Iwasaki K, Oishi R, et al. (2012) Involvement of opioid system in cognitive deficits induced by  $\Delta^9$ -tetrahydrocannabinol in rats. *Psychopharmacology (Berlin)* 219: 1111-1118.
94. Englund A, Morrison PD, Nottage J, Hague D, Kane F, et al. (2013) Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol* 27: 19-27.
95. Wright MJ Jr, Vandewater SA, Taffe MA (2013) Cannabidiol attenuates deficits of visuospatial associative memory induced by  $\Delta(9)$  tetrahydrocannabinol. *Br J Pharmacol* 170: 1365-1373.
96. Filbey FM, Aslan SD, Calhoun VD, Spence JS, Damaraju E, et al. (2014) Long-term effects of marijuana use on the brain. *Proc Natl Acad Sci USA* 111: 16913-16918.
97. Burggren AC, Siddarth P, Mahmood Z, London ED, Harrison TM, et al. (2018) Subregional hippocampal thickness abnormalities in older adults with a history of heavy cannabis use. *Cannabis and Cannabinoid Res* 3: 242-251.
98. Orr C, Spechler P, Cao Z, Albaugh M, Chaarani B, et al. (2019) Grey matter volume differences associated with extremely low levels of cannabis use in adolescence. *J Neurosci* 39: 1817-1827.