**REVIEW ARTICLE**

# DOES CANNABIS CONSUMPTION NEGATIVELY AFFECT COGNITION? A REVIEW OF THE SCIENTIFIC EVIDENCE

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**Abstract**

***Objective:*** **This review summarises the existing evidence on the effects that recreational and medical use of cannabis and cannabinoids have on cognitive performance.** ***Methods:*** **Databases (PubMed, Medline, and Google Scholar) were searched from inception to March 2017 by adopting the following key terms: dronabinol, nabilone, nabiximols, cannabis, marijuana, cognition, neurology, and neuropsychology. A total of 94 documents, including reviews, preclinical and clinical studies, industrial and government agencies reports were included in this review.** ***Results:*** **We found that recreational use of cannabis doubles the risk of a fatal traffic accident by impairing attention and lengthening reaction time. Short-term use lowers performance in working memory, attention, executive functions and visual perception tasks. Chronic recreational use in adolescents also doubles the risk of early school-leaving, cognitive impairment and psychoses in adulthood. Adverse effects of cannabis-based medication – dronabinol, nabiximol and nabilone – and ingestion/inhalation of marijuana allowed for medical use include dizziness, drowsiness and short-term memory impairment.** ***Conclusion:*** **Cannabis consumption is associated with significant impairments in a range of cognitive abilities. Of particular concern, early and chronic exposure to cannabis, especially in the adolescence, seems to be associated with irreversible cognitive impairments.** ***ASEAN Journal of Psychiatry, Vol. 18 (2): July – December 2017: XX XX.***

**Keywords: Cannabis, Cannabinoids, Cognition, Neuropsychology**

## Introduction

"Cannabis" is frequently adopted in reference to the flowering tops of the female *Cannabis sativa* plant. Cannabis is usually smoked or ingested to achieve the desired psychoactive effects of euphoria and increase sociability. Such effects are primarily produced by delta-9-tetrahydrocannabinol (THC) and are modulated by cannabidiol (CBD), a non-psychoactive cannabinoid [1]. The more general term "cannabinoids" is used in reference to three different classes of active compounds that exhibit effects, especially in the central nervous system (CNS) and immune system: (i) phytocannabinoids, which are the constituents of *Cannabis sativa* and include, among others, THC and CBD, (ii) endocannabinoids, which act as neuromodulators and neurotransmitters in the human body and (iii) synthetic cannabinoid preparations, of which three are currently approved for medical use – dronabinol (Marinol), nabiximol (Sativex) and nabilone

(Cesamet) – and seven are still under development by the pharmaceutical industry: dexanabinol, CT-3, cannabinor, HU 308, HU 331, rimonabant, taranabant [2, 3].

Phytocannabinoids and synthetic cannabinoids are used in medicine to ease chemotherapy-related nausea and vomiting, chronic pain, neuropathic pain, muscle spasm, anxiety and sleep disturbances. Other proposed medical use include anti-inflammatory activity, antiviral activity and antitumoral activity [4]. Endocannabinoids are a class of bio-active lipids that serve as natural ligands of the cannabinoid receptors. Anandamide (*N*-arachidonylethanolamide, AEA) was the first of such ligands to be isolated, in 1992, followed by 2-arachidonoylglycerol (2-AG) [5]. More recently, three more endocannabinoids were identified: 2-arachidonyl-gliceryl-ether (noladin, 2-AGE) [6], virodhamine (*O*-arachidonyl ethanolamine) [7] and *N*-arachidonyl dopamine (NADA) [8].

Endocannabinoids are synthesized in the post-synaptic terminals of neural cells and bind to the cannabinoid receptors in near-by cells or in the same cells that synthesized them [9]. The two most relevant receptors for cannabinoids are the $CB_1$ and $CB_2$, predominantly expressed in the Central Neural System (CNS) and immune system respectively [10]. Once released, endocannabinoids are inactivated via reuptake, hydrolysis or absorbed within the phospholipidic layers of the cellular membrane [11]. Endocannabinoids serve as a neuromodulator system that controls neural excitability by either initiating a second messenger cascade reaction or by interacting with gamma-aminobutyric acid-ergic (GABA-ergic), serotoninergic, glutamatergic or dopaminergic transmission [12].

The physiological role of the endocannabinoids system is very diverse. It controls appetite by increasing hunger after endocannabinoid binding with the central $CB_1$ receptors in the hypothalamus [13]. It is also involved in the extinction of old memories by suppressing long-term potentiation in the hippocampus[14]. Endocannabinoids also possess antiemetic [15], analgesic [16], anticonvulsive [17], and hypotensive properties [18]. They also seem to modulate immune [19] and stress responses [20], control energy balance [21], promote sleep [22] and lower spasticity associated to multiple sclerosis [23]. This review collects the evidence on the cognitive risk associated with the early, short-term and long-term assumption of cannabis for medical and/or recreational reasons.

## Methods

### *Types of Studies*

Randomized clinical trials (RCTs) comparing cannabinoids with usual care, placebo or no treatment in various patient populations were included in this review. Non-randomized, non-controlled studies were also reviewed when including at least 25 participants. *In vitro*, *in silico* and animal studies on endocannabinoids signalling and endocannabinoids receptors were also included when pertinent to explore the effects of suppression/enhancement on cognition.

In addition, scientific literature reviews, industry reports and government reports on the adverse effects of cannabis on cognition in patients and healthy individuals who reported recreational use of cannabis were reviewed. Any anecdotal literature, which was prevalent in Google Scholar searches, was excluded from the review.

### *Types of Participants*

Studies with participants of any age and gender consuming cannabis in any of the following situations were included: (i) chemotherapy-induced nausea and vomiting; (ii) appetite stimulation in HIV/AIDS, (iii) chronic pain, (iv) spasticity due to multiple sclerosis (MS) or paraplegia, (v) depression, (vi) anxiety disorders, (vii) post-traumatic stress disorder, (viii) sleep disorders, (ix) psychosis, (x) intraocular pressure in glaucoma, and (xi) neurological disorders (amyotrophic lateral sclerosis, dystonia, Huntington's disease, Parkinson's disease, Tourette's syndrome).

### *Types of Consumption/Intervention*

Studies exploring the association between cognitive performance and any form of

medical or recreational cannabis consumption were included in the review: smoked/ingested phytocannabinoids or administered synthetic cannabinoids.

### *Search Strategy*

The literature review was conducted in June 2015 and updated continuously until March 2017 using three popular databases: PubMed, Medline and Google Scholar. Relevant literature was generated by using key search terms in several different combinations to retrieve as many publications as possible. The comprehensive list of search terms used included dronabinol, nabilone, nabiximols, cannabis, marijuana, hashish, cognition, neurology, neuropsychology, prenatal.

## Results

From the PubMed, Medline and Google Scholar database searches a total of 70 publications were included to identify trend in the association between recreational and medical use of cannabisand cognition. It is worth noting that "medical use" may include the administration of cannabis-derived pharmaceutical formulations as well as cannabis ingested or inhaled under medical control: reference to either case is specified below.

### *Acute Exposure to Recreational Cannabis and Neuropsychological Functioning*

The acute effects of cannabis use (between 5 and 36 occasions of cannabis use in a year) on cognition have been reviewed by Lundqvist [24] and are very well documented. Such use lowers performance in neuropsychological measures of verbal memory, attention, short-term memory, executive functions, visual perception, facial emotion recognition, memory consolidation and retrieval [25-30]. Verbal memory, attention, episodic memory consolidation and working memory in particular, seem to be consistently impaired by both acute and chronic exposure to cannabis [31], in a dose-dependent fashion [32, 33]. These findings are in line with those obtained in studies administering THC intravenously on non-users: poorer immediate and delayed verbal recall and poorer verbal working memory was noted 10 minutes after drug-administration [34, 35].

A study comparing psychomotor performance across a group of occasional users and chronic users engaged in a driving simulation task intuitively showed that both users were significantly impaired compared to non-users but – counter-intuitively – occasional users were more impaired than chronic users, perhaps as a result of a more cautious behaviour in the chronic users, who were more aware of their level of intoxication [36, 37]. Recent systematic reviews and meta-analyses concluded that acute cannabis use is associated with a two-[3, 38, 39] to seven-fold [40] risk of being involved in a fatal accident.

### *Acute Exposure to Medical Cannabis and Neuropsychological Functioning*

The most frequently reported adverse events reported in clinical trials after acute administration of dronabinol (Marinol©) and nabiximols (Sativex©) – drowsiness, dizziness, transient impairment of sensory and perceptual functions [41, 42] – involve the Central Nervous System (CNS). These effects were reported in 24% of patients receiving Marinol© as an anti-emetic and 8% of patients who were administered it as an appetite stimulant [41]. Dizziness is the most common adverse event reported with Sativex©, with 25 to 35% of patients reporting it [43].

Acute administration of nabilone or nabiximols has been found to impair psychomotor performance crucial in driving behaviours: the learning and execution of coordinated movement of the hands, fingers, upper and lower limbs. Acute administration of a medium dose of dronabinol (20 mg) or THC from hemp milk decoctions (16.5 mg) was also found to lower performance in a set of motor and perceptual tasks required for safe driving [44-46]. Performance deterioration after administration of dronabinol is comparable to the one observed in drivers with a blood-alcohol concentration of 0.8 mg/mL (0.08 g%): serum THC concentrations between 2 and 5 ng/mL have been identified as a threshold above which THC-induced impairment of skills related to driving become apparent [47-49]. Decrease in performance is dose-dependent: the driving skills deteriorate

with increasing dosages of dronabinol, especially in occasional users [50]. Driving performance impairment was reported to be highest during the first hour after inhaling cannabis and declines after 3-4 hours [51, 52].

### *Chronic Exposure to Recreational Cannabis and Neuropsychological Functioning*

Findings on the long-term effects of chronic, recreational cannabis consumption (1 to 3 joints per day, more than 160 times per year) on cognitive performance are heterogeneous. While some studies suggest that lower cognitive performance is associated to either chronic use [53-55] or abstinence after chronic use [25, 27], other studies could not confirm these associations [56-58]. Nonetheless, most of the evidence collected so far suggests that chronic cannabis use leads to potentially long-lasting impairment of verbal learning, memory and attention [46, 59-62].

A global neuropsychological decline was observed in a longitudinal study tracking 1037 chronic cannabis users who started using during adolescence and were followed up for 20 years. Importantly, cessation of cannabis use for one month to one year did not restore the loss in cognitive functioning [25, 63, 64]. Chronic cannabis use seems to be most likely to affect cognition in early-onset users [65, 66]: such early-onset, chronic use affects learning abilities, executive function, working memory and verbal memory, independently from other substances of abuse like tobacco and alcohol [30, 65, 67-71]. Also, cognitive performance seems to decline in line with cannabis' cumulative, lifetime exposure: in a verbal memory task, for example, every 5 years of past exposure were associated with 1 fewer recalled word from a list of 15 [71].

Studies on the long-term neuropsychological sequelae of prenatal exposure to recreational heavy-use (one or more cigarettes per day) of marijuana have reported significantly lower speed of processing and visual motor coordination performance in the offspring at the age of 16 [72], lower Stanford-Binet Intelligence Scale IQ scores in children at 3 [73] and 6 years of age [74], lower Continuous Performance Task working-memory and learning performance[75], and lower executive functions performance [76].

Findings on the effect of chronic cannabis use on general intelligence are mixed, with one [70] study supporting a lower general intelligence in users and one study [77] finding no association. Cognitive disruptions are more likely in early, chronic, frequent users [78-80]. These users perform approximately one-third of a standard deviation lower compared with their non-user peers [81].

### *Chronic Exposure to Medical Cannabis and Neuropsychological Functioning*

In the animal model, acute administration of dronabinol was found to impair working memory in an object recognition task [82] and attention [61, 83, 84]. In multiple sclerosis patients who ingest or inhale cannabis, it was observed poorer performance in tasks probing working memory, executive functions, visuo-spatial perception and speed of information processing [85]. Driving performance is also impaired in heavy, chronic users of dronabinol, and the level of impairment on dosage level [50].
Studies exploring the impact of chronic exposure to medical cannabis on cognition found effects similar to those of chronic, recreational use: it is worth noting that participants in these studies are often also recreational users [86].

## Discussion

The literature on the effect of cannabis exposure on cognition is generally heterogeneous in terms of length of exposure to cannabis and types of participants assessed. The effects of cannabis exposure on cognitive performance depend on the onset of consumption, on the type of consumption (medical vs. recreational; smoked vs. ingested; direct or indirect), on the age of the consumer, on the duration and quantity of consumption, on the potency of cannabis consumed. Also, cognitive domains that are crystallized under the same "umbrella term" (e.g. "executive function" or "memory") reflect cognitive processes that recruit distinct populations of neurons in different brain districts and are measured by neuropsychological tools that not always are equivalent to each other [87].

Despite the above mentioned heterogeneity of scopes, samples and measuring tools, the

evidence to support a negative impact of THC on cognition seems robust. Early, chronic, recreational consumption of cannabis, in particular, is generally found to exert deleterious effects on learning abilities, executive function, working memory, verbal memory [30, 65, 67-71] and general intelligence [78-80]. Often, these effects are directly proportional to the frequency and duration of cannabis consumption [71].

Prenatal exposure to recreational, heavy use of cannabis also exerts particularly deleterious effects on the offsprings' general intelligence [73, 74, 88], learning abilities [75], working memory and executive functions [76]. Studies on the effects of the acute exposure to cannabis bear more mixed findings, possibly due to differences in the means of administration and methodological difficulties in the investigation of long lasting effects on cognition of acute administration of cannabis on non-regular users. Impairment of verbal and working memory has been consistently found among non-users or occasional users after acute administration of THC, either intravenously or by inhalation [34, 37]. Interestingly, when groups of frequent users and occasional users were compared on a battery of neuropsychological tests after acute THC administration, the occasional users showed a higher degree of impairment in tasks associated with driving skills [39, 50], and such impairment is amplified when cannabis is administered in combination with alcohol [36, 89].

Investigations on the long-term, permanent neuropsychological sequelae of chronic cannabis use are particularly challenging due to the considerable resources required. Most of these investigations have been conducted on small samples and only collected their measures at baseline [54, 57, 90]. While some studies have been conducted on relatively large samples including baseline and follow-up measures after a period of abstinence[27], very few investigations have employed a longitudinal design on very large samples followed up for up to forty years. Regardless the design and sample size, all these studies have found that the cognitive decline associated with chronic cannabis use spanned a wide array of cognitive domains, from memory to executive functioning to learning, and the severity of the decline was proportional to frequency and years of use [54]. The evidence from follow-up studies suggest that chances for cognitive impairment to recover in chronic cannabis users depend on age of use onset: cognitive decline is not reversed after use cessation in individuals who started consuming during adolescence [63, 91, 92]. On the other hand, in young adults who were heavy users, abstinence for 12 months restored their cognition to levels not significantly different from non-users [93].

Lack of control for combined consumption of cannabis with other substances of abuse like alcohol, tobacco and amphetamines, common in cannabis users, is one of the most frequent limitations in the available literature. Alcohol has a potentiating effect on the cognitively impairing properties of THC: especially in tasks associated with driving skills and divided attention [60]. When combined with alcohol consumption, the cognitively impairing effects of THC are potentiated in frequent cannabis users [94]. Other frequent limitations found in the available literature refer to the lack of control for premorbid functioning and lack of information on the participants' educational level. A final general limitation of the reviews available on the effects of cannabis on cognition focuses on the lack of standardization on cannabis use metrics across studies: active principles' combination (THC/CBD), potency, frequency of use, duration of use and length of abstinence [31].

Despite the above-mentioned limitations, the available evidence on the impact of cannabis consumption on cognitive function and development suggests that medical practitioners must exercise care with patients who seek prescription of medicinal cannabis. Still, public acceptance, rather than science, has been the main drive to push approval of medical cannabis in some regions in the West and in the Asia-Pacific region. Regulations on prescription, monitoring, informed consent, record-keeping, right to refuse treatment, sourcing and supply of medical cannabis, vary from state to state: complaints to government and professional bodies and criminal law issues may arise in situations when patients who are on cannabis medications prescribed in states where medicinal cannabis is regulated seek continuation of treatment in states where

medical cannabis is not allowed and regulated [95]. The evidence for pharmacological interactions between psychiatric medications like neuroleptics and antidepressants and cannabis-derived compounds suggests extra-care in the management of patients seeking medicinal cannabis prescription while under psychiatric care [34].

Medical practitioners should consider laws and regulations by their own government and professional body, and perhaps consult legal experts within their own institution, before seconding a patient's request for medical cannabis treatment [96].

## Conclusion

There is solid and consistent evidence on the association between early, chronic cannabis use and lower cognitive performance. The strength of this association is often dose-dependent, persists after statistical adjustment for plausible confounding factors and is also observed in children and young adults who were prenatally exposed to cannabis.

Acute cannabis consumption – in the form of either phytocannabinoids or synthetic cannabinoids - dramatically increases the risk of fatal car crashes. Chronic cannabis consumption in early use onset individuals is also associated with long lasting, and irreversible impairment of verbal learning, working memory, executive functions, visuo-spatial perception and attention.

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