Recent Update of cannabinoids effect on the body

Essay

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M.B.B.CH

For partial fulfillment of master degree in neurology and psychiatry

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2014

Acknowledgment

First of all, all gratitude is due to **God** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to **Prof. Dr. Tarek Assad Abdo** *Professor of Neuropsychiatry, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

I am eternally grateful to **Prof. Dr.Abeer Mahmoud Eissa,** *Professor of Neuropsychiatry, faculty of medicine, Ain Shams University, for her help and keep support, without her help this work would have never been completed. I am deeply indebted to him for her scrutiny, her comments and suggestion and her deep interest in the subject..*

I would like to express my deepest gratitude to **Dr. Doha Mostafa El Serafy** *Assistant professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for her kind advice support and valuable supervision and her great effort throughout this work.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Ahmed Mohamed Nabih Degheady

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AD	Alzheimer dementia
ADHD	Attention deficit hyperactivity disorder
AED	Antiepileptic drugs
AIDS	Acquired immune deficiency syndrome
ASPD	Antisocial personality disorder
BPRS	Brief psychiatric rating scale
CB	Cannabinoid
CBD	Cannabidiol
COMT	Catechol-0-methyltransferase
CNS	Central nervous system
CRF	corticotrophin-releasing factor
CSF	Cerebrospinal fluid
CT	Computed tomography
CU	Cannabis use
CUD	Cannabis use disorder
CyP	Cytochrome P enzyme
D	Dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision

	Early developmental stages of psychopathology
EDSP	Functional magnetic resonance imaging
fMRI	Human immunodeficiency virus
HIV	International Classification of Diseases, Tenth
ICD-10	Revision
IOP	Intraocular pressure
LHRH	Leutinizing hormone releasing hormone
l-LPFC	left lateral prefrontal cortex
MINI	Mini international neuropsychiatry interview
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NGF	Nerve growth factor
NIDA	National institute of drug abuse
NMDA	N-methyl-Daspartate
PCP	Phencyclidine
PET	Positron emission tomography
RCT	Randomised controlled trials
r-DLPFC	right dorsolateral prefrontal cortex
r-OFC	right lateral orbitofrontal cortex
SANS	Scale for assessing negative symptoms
THC	Tetrahydrocannabinol
UK	United kingdom
USA	United States of America
WHO	World Health Organization

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Introduction

Cannabinoids are present in the stalks, leaves, flowers and seeds of Cannabis sativa, Cannabis indica and Cannabis ruderalis plants, and also in the resin secreted by the female plant. Herbal cannabis contains over 400 compounds including over 60 cannabinoids **(*World Health Organization,*1997).**

Cannabis sativa is one of the oldest crops and has been cultivated for more than 4,000 years for the production of fibers and for medical and recreational purposes. The earliest written reference to it is found in the 15th century BC Chinese pharmacopeia, the 'Rh-Ya'. In Central Asia, India and the Middle Eastern region, the use of cannabis preparations for headache, abdominal pain and cramps was popular and part of the folk medicine. In the late 18th century, the medical use of cannabis or Indian hemp' was reintroduced to Western medicine by the British physician William O'Shaughnessy, who had recognized its therapeutic value during his work in Cal-cutta. Even Queen Victoria was prescribed cannabis by her physician for the treatment of her menstrual pain **(Kraft, 2012).**

Plant extracts were used in Europe and the USA for the treatment of rabies, tetanus, convulsions, menstrual cramps and headache and were even part of the US pharmacopoeia until 1942. Today, only-tetrahydrocannabinol (THC; Marinol ,dronabinol),

Nabilone , a synthetical analogue of THC, and an oromucosal spray containing THC and cannabidiol [cannabis-based medi-cine (CBM); Sativex] are approved in several countries and available for medical purpose**(Grotenhermen and Müller-Vahl ; 2012)**

Cannabis is the most commonly used illicit drug in the United States with over 16.7 million users in 2009 The 18–25 year old age group has the highest prevalence of marijuana use. Each year 2.6 million `Americans become new users. The majority of these individuals are less than nineteen years of age. Similarly in Europe, cannabis use is prominent among young adults, with a prevalence that has increased from 5% in 1990 to 15% in 2005 . While the overall prevalence of marijuana use has remained stable in the United States at 4%, the prevalence of cannabis use disorders (i.e. cannabis dependence, cannabis abuse) has continued to rise. Risk factors for developing cannabis use disorders include male race, lower income, living in a Western culture, and being separated, divorced, or widowed **(Galli et al; 2011).**

Cannabinoids are highly lipophilic molecules that have been shown to alter the functional activities of immune cells *in vitro* and *in vivo*. The term "exogenous cannabinoid" has been applied to cannabinoids that are extracted from the marijuana plant *Cannabis sativa* or are synthesized in the laboratory. Delta-9-

tetrahydrocannabinol (Δ^9-THC), cannabinol(CBN), and cannabidiol (CBD) have been the most studied exogenous cannabinoids. Δ^9-THC is the major psychoactive and immunomodulatory component in marijuana and has been attributed primarily as exerting immunosuppressive effects on immune cells at peripheral sites and within the central nervous system (CNS)**(Cabral and Griffin-Thomas, 2009).**

Cannabinoids receptors:

Two distinct cannabinoid receptors, CB_1 and CB_2, have been identified in human and animal models. The CB_1 and CB_2 receptors function as G-protein coupled receptors that act by inhibiting adenylatecyclase .In the brain, CB_1 receptors are localized to the cerebral cortex, hypothalamus, anterior cingulate gyrus, hippocampus, cerebellum, and basal ganglia . In the gastrointestinal system, CB_1 receptors are found on both intrinsic and extrinsic neurons, with the enteric nervous system serving as the major site of action. Other organs where CB_1 receptors have been identified are the spleen, heart, liver, uterus, bladder, and vas deferens. In comparison, much less is known about the effects of the CB_2 receptor. CB_2 receptors are expressed primarily by immune cells. In the gastrointestinal system, CB_2 receptors are expressed by lamina propria plasma cells and activated macrophages, as well as by the myenteric and submucosal plexus ganglia in human ileum . CB_2 receptors are likely involved in the

inhibition of inflammation, visceral pain, and intestinal motility in the inflamed gut**(Galli et al;2011).**

Cannabinoids effect on body:

Much of the early research assessing the effects of cannabis on driving performance was done by laboratory and driving simulator studies. The results of these studies are generally consistent: at increased doses, cannabis impairs the psychomotor skills necessary for safe driving. However laboratory studies have high internal validity with regard to the dose related effects of cannabis on performance, the dose-response association is unclear in relation to driving ability and collision risk outside the laboratory. As a result, these studies do not always translate well to driving scenarios in the real world, and generally focus on experienced cannabis users consuming the drug in unorthodox surroundings and undertaking tasks that do not always reflect the complex nature of driving in natural settings**(Asbridge et al; 2012)**

Whereas adult users appear comparatively immune to cannabis-induced behavioral and brain morphologic changes, the same cannot be said of individuals initiating use during their early teens, when effects are both more severe and more long-lasting than in adults. During puberty, a period characterized by significant cerebral reorganization, particularly of the frontal lobes implicated in behavior, the brain is especially vulnerable to

adverse effects from exogenous cannabinoids. How they interfere with this remodeling process during what Schneider calls a "sensitive period" is unknown, although Bossong and Niesink propose that exogenous cannabis use can induce schizophrenia during late brain maturation through physiologic disruption of the endogenous cannabinoid system that modulates glutamate and γ-aminobutyric acid release in prefrontal neurocircuitry, an iteration of the hypothesis of van Os et al. Furthermore, in keeping with the epigenetic hypothesis of Henquet et al, carriers of a specific polymorphism of the catechol oxidase methyltransferase gene (*COMT*valine 158 allele) are especially likely to develop psychotic symptoms or full-blown schizophrenia, an effect attenuated or eliminated if cannabis use is delayed until after brain maturity**(Bostwick, 2012)**.

Coinciding with the increasing rates of cannabis abuse has been the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome. Cannabinoid Hyperemesis Syndrome is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and frequent hot bathing. Cannabinoid Hyperemesis Syndrome occurs by an unknown mechanism. Despite the well-established anti-emetic properties of marijuana, there is increasing evidence of its paradoxical effects on the gastrointestinal tract and CNS. Tetrahydrocannabinol, cannabidiol, and cannabigerol are three cannabinoids found in the

cannabis plant with opposing effects on the emesis response. The clinical course of Cannabinoid Hyperemesis Syndrome may be divided into three phases: prodromal, hyperemetic, and recovery phase. The hyperemetic phase usually ceases within 48 hours, and treatment involves supportive therapy with fluid resuscitation and anti-emetic medications. Patients often demonstrate the learned behavior of frequent hot bathing, which produces temporary cessation of nausea, vomiting, and abdominal pain. The broad differential diagnosis of nausea and vomiting often leads to delay in the diagnosis of Cannabinoid Hyperemesis Syndrome. Cyclic Vomiting Syndrome shares several similarities with CHS and the two conditions are often confused. Knowledge of the epidemiology, pathophysiology, and natural course of Cannabinoid Hyperemesis Syndrome is limited and requires further investigation **(Galli et al;2011).**

With regard to cannabis as a "gateway" drug, its regular or heavy use in adolescence is clearly associated with increased risk for both abuse and dependence on other illicit drugs. Neither causality nor directionality has been proven, however. Cannabis use may simply be a marker for deviant behavior, with the tendency to advance to harder drugs the result of their simply being available. In what has been called a "reverse gateway," cannabis use weekly or more often predisposes adolescent users to

more than 8 times the risk of eventual tobacco use and progression to nicotine dependence**(Bostwick, 2012).**

Cannabinoids and psychiatric disorders:

In the area of mental health, recent research has analyzed the relation between cannabis and psychotic disorders and their course, which is the aspect that has attracted most interest, and has tried to control for the diverse contaminating factors that mediate the relation between cannabis use and affective disorders. In addition, the effects of cannabis on cognitive deterioration or antisocial behavior, classically associated with cannabis users, have been analyzed. Research has also been conducted into the well-known "amotivational syndrome," although it has received less attention and fewer conclusions have been reached(**Fernández-Artamendi et al;2011)**

Marijuana continues to have the reputation among the general public as being benign, non–habit-forming, and incapable of inducing true addiction. For most users this may be so. Experimentation with marijuana has become an adolescent rite of passage, with the prevalence of use peaking in the late teens and early 20s, then decreasing significantly as youths settle into the adult business of establishing careers and families. With a lifetime dependence risk of 9% in marijuana usersvs 32% for nicotine, 23% for heroin, 17% for cocaine, and 15% for alcohol, the addiction risk with marijuana is not as high as that for other drugs

of abuse. Unlike cocaine dependence, which develops explosively after first use, marijuana dependence comes on insidiously. Marijuana use typically starts at a younger age than cocaine use (18 vs 20 years of age). The risk for new-onset dependence is essentially zero after the age of 25 years, whereas cocaine dependence continues to accrue until the age of 45 years. Likewise, the average age at first alcohol use is the same as for marijuana, but alcohol users will keep on making the transition from social use to dependence for decades after first use.

Like all addictive drugs, marijuana exerts its influence through the midbrain reward center, triggering dopamine release in the prefrontal cortex. Although its existence was questioned until recently, a withdrawal syndrome is increasingly appreciated, characterized by irritability, anxiety, anorexia and weight loss, restlessness, disturbed sleep, and craving **(Bostwick, 2012).**

The association between cannabis and psychosis not withstanding, the question of whether cannabis causes psychosis remains unresolved, even as evidence mounts that its use worsens the course of psychotic illness. In an Australian cohort, Degenhardt et al tested 4 hypotheses regarding the association between cannabis use and schizophrenia, including that cannabis use (1) may cause schizophrenia in some patients, (2) may precipitate psychosis in vulnerable individuals, (3) may exacerbate symptoms of schizophrenia, or (4) may be more likely in