



Cannabis : Joins of Mental Illness

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ABSTRACT

With the increasing push to legalise cannabis in western nations there is an estimation that the potential impact of this policy change on vulnerable population such as those with mental illness, including schizophrenia, mood and anxiety disorders. Cannabis is the most likely used illicit drug worldwide. Cannabis sativa is an important herbaceous species originating from central Asia which has been used in folk medicine. Despite the widespread use of cannabis among young people little research attention has been given to the development of psychometrically sound measures specific to cannabis related problems. The laws governing cannabis are evolving worldwide are associated with changing pattern of use. Patients with a serious mental illness often use cannabis at higher rates than the general population. Cannabis may induce or exacerbate a number of mental health problems. The main psychoactive drug in cannabis is Δ^9 tetrahydrocannabinol (THC). Cannabidiol, a non-toxicating cannabinoid found in some forms of cannabis, may offset some of these acute effects. Chronic use of cannabis is associated with psychiatric, respiratory, cardiovascular and bone effects. It also has oncogenic, teratogenic and mutagenic effects, all of which depend upon dose and duration of use. The present article mainly reviews about the association between cannabis and mental health.

Keywords: Homomeric nicotinic receptors, Antiquity, Cannabidiol, Psychosis, Cannabinoid hyperemesis syndrome.

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INTRODUCTION

Cannabis is one of the most extensively used recreational and illicit drugs in the world as well as accounts for 80% of the 200 million users in the world.¹⁻⁶ Cannabis abuse is a widespread phenomenon in western societies, specially among teenagers and young adults.⁷ Cannabis dependence criteria are described by the principal diagnostic manuals (DSM-IV and ICD-10).⁸ Uptake of cannabis typically occurs during the mid to late teens while individuals are yet attending school.² Earlier age of initiation and greater complication with cannabis has been associated with increased risk of mental health problems, other substance use disorders, criminal offending, poorer educational attainment and school drop-out.⁵ Cannabis has been an object of disparate fear and praise throughout the centuries in relation to the predominant culture and policy.⁸ There is growing evidence of an association between mental health problems and cannabis use. What persist unclear is whether the proper elucidation of this indication is that cannabis use causes mental health problems.² Use among girls at this age was strongly related to concurrent antisocial behaviour.⁹ The main

psychoactive substance in cannabis is Δ^9 -tetrahydrocannabinol (THC).¹⁰ The acute response to cannabis generally includes euphoria, anxiety feeling of detachment, cognitive dysfunction, impaired psychiatric performances.^{4,10,11} Depression often preceded the substance use.⁹ The neural basis for the cognitive deficits associated with cannabis abuse is unknown and predictably complex.¹¹ Prevalence of cannabis use, dependence, and treatment seeking, little research attention has been given to developing psychometrically sound measures specific to cannabis-related problems.⁵ Treatment seeking rates for cannabis use problems have also risen internationally over the past decade.⁵ Homomeric 7 nicotinic receptors are novel molecular entities that could be targeted in the development of new drugs for the treatment of cannabis dependence.⁷

History

Cannabis sativa L. is possibly one among the oldest plants cultivated by man, but has remained a source of controversy throughout its history.¹² Perhaps the first references to the medicinal use of cannabis are established in the Chinese pharmacopoeia of Emperor Shen-Nung, written in 2737 BC.¹³ Cannabis is that the at most ordinarily cultivated, trafficked, and exploited illicit drug worldwide.¹⁴ The cannabis or hemp plant has been known for antiquity and grows in almost all parts of the world.¹⁵ Historically, cannabis medical applications appear to possess been realized by most cultures.¹⁶ This utilization of cannabis continued in the West till the mid-1880s and continues today in parts of Asia.¹³ Humans have utilized



cannabis products in various forms throughout recorded history.¹² The introduction of the drug effects of cannabis into Europe in the 19th century followed various routes for the medical and nonmedical utilizations.¹⁵ In the U.S., cannabis was widely utilized as a medicine during the 19th and early 20th centuries, described within the US Pharmacopoeia for the primary time in 1850.¹⁴ Egypt is universally recognized as one of the great early civilizations, with an advanced medical system.¹² Cannabis' therapeutic uses were first introduced to Western medicine in 1839.¹⁶ Although cannabis features a long history of therapeutic use, in both traditional and Western medicine, it fell into disuse almost a century ago, when it had been superseded by more stable, reliable and effective new synthetic medications.¹⁵ Over the past few thousand years many different cultures have been exposed to cannabis and often noticed the medicinal application of cannabis.¹⁶ The utility and undertaking of medicinal cannabis pursued to evolve, as manifested by the developing number of states now permitting use for certain medical indications.¹⁴

Epidemiology

Cannabis grows in about every country within the world.¹⁷ The primitive users within the history of cannabis be the Indians.¹⁸ Cannabis is wide spread in developed and developing countries. Global patterns of cannabis use are approximated by the United Nations Office on Drugs and Crime (UNODC).¹⁹ Cannabis use is almost widespread in West and Central African Republic (13.2 percent, 34.3 million users), Northern America (12.9 percent, 41.5 million users), and Oceania (11.0 percent, 2.9 million users), and slightly prevalent in East and South-East Asia (0.6 percent, 9.7 million users), East and South-East Europe (2.4 percent, 5.5 million users), the Caribbean (2.2 percent, 630 thousand users), and Central America (2.8 percent, 820 thousand users).¹⁷ Cannabis use seems least common in Africa, Asia and South and Central America.²⁰ Today, there's no a part of the planet that's free from the curse of drug traffick and white plague. Globally 2% cause-specific disfunction adjusted life years for children are attributed to illicit drug.¹⁸ Prevalence of cannabis use is highest for young adults and men.^{18,20} During the past four decades, cannabis potency, specified by the THC content in seized samples, has roughly enlarged worldwide.²¹ Cannabis dependence potentially a primarily experienced by young adults, particularly in higher income countries.¹⁹ Cannabis has been utilized in the United States since the 1800s.²² US surveys estimate substantial comorbidity of CUDs with mood (39.6%), anxiety (30.5%) and personality (35.9%) disorders.²⁰ In the past 10 years, much has been learned about cannabis, its use, and its consequences.²¹ Current evidence indicates that quantity of use, the use of synthetic cannabis, age, gender, comorbidities.²⁰ Concerns about the risks of adolescent cannabis use, especially regular or heavy use, specialise in the developing adolescent brain.²¹ Evidence concerning other cognitive domains and neurological consequences, as well as cerebrovascular events, is restricted and inconsistent.²⁰

Cannabis use epidemiology, regarding age and sex patterns for the disease, differences in prevalence between regions, and differ in these parameters along time.¹⁹

Toxicology

Cannabis is the habitually used drug in the worldwide, and its rate of use is booming as legalization for recreational and medical use continues to rise according to the 2018 United Nations World Drug Report.²² The dose-related toxicity of the main psychoactive component of cannabis in brain regions is abundant in cannabinoid CB1 receptors is common in animal studies.²³ Cannabis use usually results in tachycardia and hypertension through sympathetic nervous system activation and parasympathetic nervous system inhibition.²² The main active substance in the cannabis plant is D9-tetrahydrocannabinol (THC) with some contribution from other cannabinoids.²⁴ In some regular but massive users cannabis causes drug dependency and is associated with psychoses and prolonged changes in mental health.¹⁹ Several studies from diverse cultures have confirmed the raised risk of psychosis and schizophreniform spectrum disorders.²⁵ The acute after effects of cannabis give rise to psyche and cognition, and to circulation. Effects of chronic use likely induces the psychosis and development of dependency to the drug.²⁶ Cannabis smoke is well known to contain several potent carcinogens including anthrocyclines, nitrosamines, polycyclic aromatic hydrocarbons, terpenes, and vinyl chloride.²⁵ Since tolerance develops to THC in the central nervous system and regarding several other effects, regular cannabis users can tolerate considerably higher doses.²⁶ Rare adverse effects are headache or nausea and vomiting.²⁶

Cardiovascular effects

Cannabis exposure is known to convict phasic systemic vasodilation, mild hypertension, and tachycardia frequently associated with postural hypotension, and a reduced duration and increased heart rate response to exercise.²⁵

The effects on the heart and wider cardiovascular system are difficult. CB1 activation leads to centrally-mediated sympathetic stimulation constantly causing marked increases in heart rate and cardiac output.²⁴

Cannabis had been linked with increased rates of cardiac arrhythmias.²⁵ THC may cause vasoconstriction of cerebral vessels and has been associated with ischemic stroke, also causes sinus tachycardia and premature ventricular beat.²⁴

Respiratory effects

Cannabis is smoked differently from tobacco. Cannabis smoke stimulates inflammation in the airways so that its continuous use is confederated with the development of chronic bronchitis. Cannabis use is associated with cancer of the lung.²⁵



Bones

Cannabinoid receptors are present on bones. Physiological studies have shown that cannabinoids have an important role in the regulation of bone density. Heavy cannabis use in humans is associated with substantial bone loss. Cannabis use is also known to be associated with profound loss of alveolar bone from the jaws.²⁵

Hormonal system and fertility

Changes in human hormone levels attributes to acute cannabis. Cannabis associated influences on the cycle length, the amount of cycles without ovulation or on the plasma concentrations of estrogens, progesterone, testosterone, prolactin, LH, or FSH in female cannabis users. On female sterility, there was a low increase of sterility risk in association with marijuana use. Reductions in male fertility by cannabis are reversible.²⁶

Maternal cannabis use and fetal development

maternal cannabis use has been shown to scale back weight at birth.²⁵ Cannabis causes embryonic or foetal malformations.²⁶ Many birth abnormalities were recognized.²⁵

The continuous use of cannabis can results in negative health impact on other organ systems, including immune system and circulation.²⁶

Chemical Constituents

Marijuana is that the crude drug derived from the plant *Marijuana L.*, a plant that's currently accepted as belonging to a family (Cannabaceae) that has just one genus (Cannabis) with only one species (*sativa*) that's highly variable.²⁷ Cannabis likely a complex plant escorted over 400 chemical entities of which entirely 60 of them are cannabinoid compounds, a total of them with opposing effects.²⁸ The best-known and thus foremost specific class of Cannabis constituents is that the C21 terpenophenolic cannabinoids, with (-)-D9-trans-(6aR,10aR)-tetrahydrocannabinol (D9-THC) being the foremost psychologically active constituent.²⁷ Many chemicals are generated in hemp through the secondary metabolism. They include cannabinoids, terpenes and phenolic compounds.²⁹ The very first compound isolated in pure form from the plant was cannabinol. The second compound found was cannabidiol (CBD). The main active compound, delta-9-tetrahydrocannabinol (d-9-THC). [28]The typical C21 group of compounds present in *C. sativa L.* is understood as cannabinoids.²⁷ Cannabis plant contains several existing phenotypes, each containing over 400 chemicals, approximately 60 are chemically unique and classified as plant cannabinoids.^{13,28} Hemp bast fibers were also found to contain cannabinoids (2% of the total metabolite extract).²⁹ Hemp seed constitutes 20-25% protein, 20-30% oil and 10-15% insoluble fibre and rich array of minerals.³⁰ The 70 known cannabinoids are often classified as, Cannabigerol (CBG) type, Cannabichromene (CBC) type, Cannabidiol (CBD) type, (-)-Δ9- trans-Tetrahydrocannabinol (D9-THC) type, (-)-D8- trans-

Tetrahydrocannabinol (D8-THC) type, Cannabicyclol (CBL) type, Cannabielsoin (CBE) type, Cannabinol (CBN) type, Cannabinodiol (CBND) type, Cannabitrinol (CBT) type, Miscellaneous types.²⁷ Natural compounds of the cannabis plant also are mentioned as phytocannabinoids of which d-9- THC is that the main psychoactive ingredient and has been widely researched both in animals and humans. It distinctively generates, during a dose- dependent manner, hypoactivity, hypothermia, spatial and verbal short-term memory impairment. Due to its higher THC content, *C. sativa* is that the preferred choice by users.²⁸ THC appear to supply the bulk of the psychoactive effects of cannabis.¹³ Most of the biological properties associated cannabinoids believe their interactions with the endocannabinoid system in humans.^{14,29} The endocannabinoid system includes two G protein- coupled cannabinoid receptors, CB1 and CB2.²⁹ Endocannabinoids are thought to modulate or play a regulatory role during a sort of physiological processing including appetite, pain-sensation, mood, memory, inflammation, insulin, sensitivity and fat and energy metabolism.^{14,29} THC is understood to be the main psychoactive component of cannabis mediated by activation of the CB1 receptors within the central system *anervosum*.¹⁴ Terpenes form the largest group of phytochemicals, with quite 100 molecules identified in Cannabis. Terpenes are liable for the odor and flavor of the varied Cannabis strains.²⁹ The other chemical constituents identified in marijuana are nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, sugar and related compounds, hydrocarbons, alcohols, aldehydes, ketones, fatty acids, esters, lactones, terpenes, flavonoids and elements.²⁷ To date, quite 540 phytochemicals are described in hemp and their pharmacological properties appear to travel much beyond psychotic effects, with the capacity to deal with needs alike the aid of chemotherapy-derived nausea and anorexia, and symptomatic mitigation of MS. Continuously discovering new prototypes of medicine is of tremendous importance to satisfy tomorrow's challenges in terms of public health.²⁹

Mechanism

Cannabis in Gastroenterology

The term 'medical cannabis' refers to the use of the cannabis plant and its constituents, known as cannabinoids, to treat disease or relieve symptoms.³¹ Exogenous cannabinoids can be produced or obtained from the Cannabis *sativa* plant. Delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two exogenous cannabinoids that are well studied and are frequently used to guide prescribing and recreational buying (CBD). THC is linked to cannabis' psychoactive and intoxicating effects, whereas CBD is non-psychoactive and appears to control THC's effects. CB1 is located in the epithelium and on some enteroendocrine cells. Animal studies have shown that activating cannabis receptors in the GI tract reduces motility, inflammation, and immunological activation. This "endocannabinoid" system



regulates gastrointestinal motility and modulates intestinal inflammation and visceral sensitivity.³²

A. Cannabis and Cannabinoids in Gastrointestinal Diseases

1) **Cannabinoids in IBD:** Cannabinoids work as endogenous anti-inflammatory agents in the gut, altering immune cell function, increasing wound healing, and lowering intestinal permeability. Both CB1 and CB2 receptor agonists, as well as THC and CBD, have been found to reduce intestinal inflammation and disease severity in animal models of colitis. In individuals with active IBD, the endocannabinoid system is changed, with studies indicating both an increase and a decrease in endocannabinoid tone. Cannabis has been reported to benefit patients with stomach pain, diarrhoea, nausea, and a loss of appetite. Cannabis appears to be useful in the treatment of IBD symptoms.^{32,33} Observational studies of cannabis in IBD patients have showed generally favourable results in terms of disease severity.³²

Mechanism: Cannabidiol (CBD) is a major component of cannabis that has no psychoactive effects but is thought to be responsible for many of the gastrointestinal effects. It has recently been shown in vitro to lower the expression of inflammatory cytokines in human colonic cells from IBD patients.³³

2) **Cannabinoids in Functional Gut Disorders:** Cannabis has long been used as an appetite stimulant and anti-diarrheal. A meta-analysis of randomised controlled trials of cannabinoid use for symptom control found evidence to support the use of cannabinoids for the treatment of chronic pain, as well as evidence that cannabinoids were linked to improvements in chemotherapy-induced nausea and vomiting, as well as weight gain in HIV infection.³²

B. Cannabis – Gastrointestinal Related Adverse Effect

1. Severe vomiting episodes have been observed in some chronic cannabis users in recent decades. Cannabinoid hyperemesis syndrome (CHS) is a recently discovered condition of cyclic vomiting associated with chronic cannabis use, who report symptom relief with cannabis withdrawal, and may be connected with pathologic bathing behaviour. It was first described in 2004 by Allen et al.^{32,33}

Mechanism: THC interacts with centrally placed CB1 receptors in the dorsal vagal complex to prevent centrally and peripherally mediated emesis. In Chronic cannabis users, downregulation of CB1 receptors in the central nervous system may impair the hypothalamic-pituitary-adrenal axis' ability to recover from stress, and cannabinoids have been shown to increase hypothalamic expression of corticotrophin releasing hormone and stress hormones (e.g., adrenocorticotrophic hormone and glucocorticoid); the combination of which may lead to dysregulation of the sympathetic nervous system.³²

Cannabis and Psychiatric Illness

Cannabis usage has been identified as one of many environmental factors linked to an individual's increased sensitivity to the development of psychotic disease, with roughly one out of every four people in this community having a concomitant CUD (cannabis use disorder) diagnosis.³⁴ With the possibility for increased cannabis usage, it's more important than ever to understand the hazards, which include the induction of psychotic and other mental symptoms in the short term. The effect of the cannabis ingredient 9-tetrahydrocannabinol (THC) alone and in combination with cannabidiol (CBD) on mental symptoms in healthy adults was investigated in a study. With significant effect sizes, a single THC administration causes psychotic, negative, and other psychiatric symptoms. There is no conclusive evidence that CBD causes symptoms or mitigates THC's effects. The Brief Psychiatric Rating Scale [BPRS] and the Positive and Negative Syndrome Scale [PANSS] are designed to track changes in symptoms across psychopathological symptom domains related to schizophrenia, including positive (psychotic-like) symptoms like hallucinations, delusions, and thought disorder, as well as negative symptoms like blunted affect, anhedonia, and amotivation, and general psychopathology including depressive, cognitive and anxiety symptoms.³⁵

Mechanism: The main psychoactive constituent of cannabis, 9-tetrahydrocannabinol (THC), has been shown to cause a significant increase in psychotic also known as positive symptoms (eg: paranoia, delusions and fragmented thinking) as well as negative symptoms, such as poor rapport, and general psychiatric symptoms, such as depression, primarily due to THC's partial agonistic effects on cannabinoid-1 receptors (CB1R's), which generates the "high" that users feel.³⁴⁻³⁶ The effects of cannabidiol (CBD), another component of cannabis, are gaining popularity. CBD by itself does not cause schizophreniform symptoms. In naturalistic investigations, cannabis with increased CBD content has been linked to fewer subclinical psychotic symptoms in adults who use cannabis recreationally. This discovery has led to speculation that CBD possesses antipsychotic characteristics, with promising outcomes in schizophrenic patients.³⁵ CBD, on the other hand, has been found in early trials to have potential therapeutic effects (e.g. antipsychotic, anxiolytic, anti-craving, pro-cognitive, and neuroprotective properties) since it appears to have different, and sometimes opposing, pharmacological effects than THC.³⁴

Cannabis and Pain Relief

The dried flowers (marijuana), fiber (hemp), resin (hashish), and oil have all been used in the treatment of pain.³⁷ Preparations of the cannabis plant, which are taken by smoking or oral ingestion, have been observed to produce analgesic, antianxiety, anti-spasmodic, muscle relaxant, anti-inflammatory and anticonvulsant effects.³¹ Historians have revealed encouraging indications to the



potential treatment of chronic pain, spasticity, cancer, seizure disorders, nausea, anorexia, and infectious disease using cannabis, but the scientific basis for its therapeutic usefulness remains unknown.³⁷ There are three types of cannabinoids. The first are phytocannabinoids, which are naturally occurring 21-carbon terpenophenolic chemicals found uniquely in *Cannabis sativa* plants, the second are endocannabinoids (present endogenously in human or animal tissues), and the third are synthetic cannabinoids. Tetrahydrocannabinol is the most well-known of these analgesics.^{31,38}

Mechanism: Cannabinoids relieve pain through a variety of receptor and non-receptor mechanisms, including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids. CB1 is found primarily in the CNS, while CB2 is found primarily in immune cells.^{31,39} Cannabinoids' analgesic action is mediated by inhibiting neurotransmitter and neuropeptide release from presynaptic nerve endings, modulating postsynaptic neuron excitability, activating descending inhibitory pain pathways, and reducing CNS inflammation.³¹ Cannabinoids, both plant-derived and endogenous, act on several pain targets in the peripheral and central nervous systems at the same time. They may relieve pain by interacting with the potential non-CB1/CB2 cannabinoid G-protein-coupled receptor (GPCR) 55 or GPCR 18 (GPR18), also known as the N-arachidonoyl glycine (NAGly) receptor; and other well-known GPCRs, such as the opioid or serotonin (5-HT) receptors.³¹

Cannabinoids as Anti-emetics

Several small clinical trials suggested that cannabinoids [tetrahydrocannabinol (THC), nabilone, and levonantradol] had clinical activity in those early days of antiemetics, though the methodologies of these studies were suboptimal. Nonetheless, given the paucity of effective antiemetic agents, the FDA approved dronabinol, a synthetic tetrahydrocannabinol, in 1985 for the treatment of nausea. Despite the use of dexamethasone, a 5-HT₃ RA, and an NK1 RA, nausea is still present in half or more of patients who receive highly emetogenic chemotherapy, indicating that there is still room for improvement. Aside from clinical trials demonstrating the efficacy of olanzapine, no new antiemetic class has been released in nearly 15 years. Furthermore, while past studies have shown that cannabis have only little single-agent efficacy, their usage in combination with the most potent antiemetics may increase antiemetic control much more.⁴⁰ The first cannabinoid agonist, nabilone (Cesamet), a D9-THC homologue, was approved for the treatment of nausea and vomiting caused by chemotherapy. Furthermore, dronabinol, a synthetic D9-THC, was introduced to the clinic as Marinol in 1985 as an antiemetic and as an appetite stimulant in 1992.⁴¹ *THC is effective against a wide range of chemotherapy regimens, including high-dose methotrexate and the doxorubicin, cyclophosphamide, and fluorouracil combination. Nabilone*

is a synthetic cannabinoid that is more efficient than prochlorperazine in reducing chemotherapy-induced emesis, including cisplatin-containing regimens. Another synthetic cannabinoid, levonantradol, is a powerful antiemetic.^{43,43}

Mechanism: While anandamide has been shown to have antiemetic activities in ferrets and least shrews, the role of 2-AG in nausea and vomiting management is less apparent.⁴¹

Cannabis Tolerance and Dependence

When a drug is stopped, the appearance of fairly predictable signs and symptoms is referred to as dependence. When the medicine is restarted or a pharmacologically comparable drug is given, the symptoms lessen or disappear. Dependence in this context does not imply addiction, increased drug seeking, or other behaviours that may be linked to dependence.⁴⁴ There is no evidence of anyone dying from 9-THC withdrawal, implying a low level of physical reliance. Physical dependency is less likely to occur than psychological dependence, abuse liability, or craving.⁴⁵ Almost every psychoactive substance creates detectable tolerance after a period of time if taken at a dose and schedule that yields sustained tissue levels. When 20mg THC was administered every 3 hours, tolerance was acquired faster than when 30mg THC was given every 4 hours. This shows that THC levels, or rapidly generated and cleared metabolites, are more important than metabolites produced more slowly and eliminated more slowly.⁴⁴

Mental Effects of Cannabis Use

Heavy repeated cannabis use, particularly during adolescence, has been associated with adverse effects, which increase the risk of mental illnesses including addiction and psychosis.^{46,47}

Acute Adverse Effects:

- (i) Troublesome experiences like anxiety, dysphoria and paranoia, especially amid naïve users.^{48,49,50}
- (ii) Depression^{49,50}
- (iii) Cognitive impairment, particularly of attention and memory
- (iv) Psychomotor impairment that could impair a person's ability to drive a motor vehicle while intoxicated.
- (v) an increased risk of psychotic symptoms in high doses, particularly among those with a personal or family history of psychosis.
- (vi) Cerebral blood flow and metabolism: One hour after smoking a 'joint', decreases in cortical CBF were remarked. Acute THC increased metabolism in the basal ganglia and the orbitofrontal cortex (OFC) and prefrontal cortex (PFC).⁴⁶



Reproductive Effects of Cannabis Use

1. Fetal development and birth defects: Several large epidemiological studies have since reported that cannabis use in pregnancy is associated with reduced birth weight and birth malformations.⁴⁸

2. Postnatal effects of maternal cannabis use: maternal cannabis use at all stages of pregnancy was associated with delinquency, problem behaviour, developmental delays in the visual system and increased tremor and startle shortly after birth.⁴⁸

Adverse Health Effects of Chronic Cannabis Use

1. Cannabis dependence^{47,48}

2. Chronic cannabis use and cognitive and brain function:

Cognitive impairment

Brain structure and function⁴⁸

3. Cannabis use and mental health:

Psychosis and schizophrenia: there were reports that regular cannabis use was associated with psychotic symptoms (disordered thinking, hallucinations and delusions), a loss of motivation, disturbed behaviour and cognitive deficits.^{48,50}

Cannabis use and other mental disorders: Several case-control and cohort studies have reported associations between cannabis use and suicide in adolescents and young adults.^{48,49,50} Several studies reported a modest association between cannabis use and depressive disorders.^{48,49}

4. Adverse health effects of long-term cannabis smoking:

Respiratory system: regular cannabis smokers reported more symptoms of chronic bronchitis than non-smokers. Regular cannabis-only smokers also found impaired respiratory function and pathological changes in lung tissue like those preceding the development of chronic obstructive pulmonary disease.⁴⁸

Cardiovascular effects: The cardiovascular risks of cannabis smoking are probably highest in older adults, but younger adults with undiagnosed cardiovascular disease may also be at risk. Accounted for clinical confirmation that cannabis smoking might paraps produce symptoms of angina in older adults with cardiovascular disease who used cannabis. Patients who had had a myocardial infarction found that cannabis use acutely increased the risk of a myocardial infarction.⁴⁸

Cannabis and (Respiratory cancers, Maternal cannabis use and childhood cancers, Male cancers)

Male Cancers: Males who smoked cannabis had an increased risk of prostate cancer and testicular cancer. The risk was higher for a non-seminoma and increased for those who began to use cannabis before the age of 18 and those who used cannabis more than weekly. It is also a

biologically believable effect that cannabinoid receptors are found in male reproductive system.⁴⁸

Maternal Cannabis Use and Childhood Cancers: Cannabis smoking during pregnancy has been associated with cancers among children.⁴⁸

Respiratory Cancers: Cannabis use could cause lung and upper respiratory tract cancers as cannabis smoke contained many of the same carcinogens as tobacco smoke. In a few case-control studies, regular cannabis smokers had shown pathological changes in lung cells of the type that precede lung cancer in tobacco smokers.⁴⁸

Treatment for Cannabis Dependence and Withdrawal

Sudden cessation of regular heavy cannabis use is associated with a distinctive withdrawal syndrome. This can include irritability, depression, anxiety, sleep problems (insomnia), restlessness, muscle pain, decreased appetite/weight loss, cravings, and a range of physical symptoms (e.g., stomach pain, shakiness/ tremors, sweating, fever, chills, or headache).^{26,51,52} There are currently no approved pharmacotherapies for cannabis dependence. Trials of several medications have occurred over recent years. A few randomized controlled trials (RCTs) and open-label studies have been conducted in clinical populations. Medications trialed includes cannabinoid CB1 receptor agonists (e.g., THC, nabilone), antidepressants, mood stabilizers, anxiolytics, α 2-adrenergic agonists, anticonvulsants, and a glutamatergic modulator.

Overall, results have shown only limited benefits, particularly in clinical populations, with only gabapentin, N-acetylcysteine, and the CB1 receptor agonists medication not only has the benefit of suppressing withdrawal, but also may attenuate the acute effects of drug use demonstrating some promise in specific patient groups.^{26,51} Dronabinol (Marinol), which is an orally administered synthetic THC in capsule form, dose-dependently reduced acute cannabis withdrawal in a laboratory study. Although, a 12-week outpatient RCT of oral dronabinol (20 mg b.i.d.) in clinical populations did not lessen illicit cannabis use. Subsequent laboratory research suggests that higher single doses of dronabinol (60 or 120 mg) may be required to reduce cannabis use. Nabilone (Cesamet), a synthetic analog of THC, possess higher bioavailability to dronabinol and also reduced cannabis withdrawal in a human laboratory study but remains untested in clinical populations. Nabiximols is an oromucosal spray which will be absorbed buccally. It consists of the extracts from Cannabis sativa plants grown under license in the UK by the company GW Pharmaceuticals. These extracts contain 27 mg/ml THC and 25 mg/ml CBD per bottle, with trace amounts of other plant-derived cannabinoids and terpenoids. Each spray of nabiximols delivers 100 mL (2.7 mg THC and 2.5 mg CBD) doses. Buccal administration provides a more rapid onset of action and more favorable pharmacokinetics than oral THC. Nabiximols is accessible in 15 countries for symptomatic



relief of spasticity in multiple sclerosis (MS) and is in development for cancer-related pain. Nabiximols have been approved in a further 12 countries.⁵¹ Nefazodone lessens anxiety and muscle pain in the course of cannabis withdrawal but had no impact on sleep disturbances or irritability.^{26,52} Mirtazapine is an antidepressant that enhances noradrenergic and serotonergic transmission by blocking presynaptic inhibitory alpha 2 autoreceptor, resulting in sedation and increased appetite.²⁶ Buspirone, the serotonin 1A partial agonist used clinically in the treatment of anxiety and augmentation of antidepressants for depressive disorders, was selected as a candidate agent in the treatment of CUD.²⁶

Gabapentin, a medication which indirectly regulates GABAergic mechanisms through its blockage of the alpha 2d subunit of voltage-gated calcium channels at selective presynaptic sites. Preclinical evidence demonstrated that gabapentin inflicts an anxiogenic-like state as a result of increased extrahypothalamic corticotrophin-releasing factor in cannabis withdrawal states, restoring brain homeostasis in the context of stress.²⁶

Medications tested include

1. Cannabinoid CB1 receptor agonists (e.g., THC, nabilone, dronabinol, cannabidiol)

a) THC - Dronabinol DOSE: 50mg/day (divided in five doses)^{7,26,51,52} 90mg/day (divided in three doses)^{7,26,51,52} Nabiximols⁵¹

b) Nabilone DOSE: 6 and 8mg/day (divided in two doses)

c) Cannabidiol DOSE: 20,400 and 800mg.²⁶

2. CB1 receptor antagonist

ex: Rimonabant DOSE: 40mg daily

3. Antidepressants (bupropion, nefazodone, mirtazapine)

a) bupropion DOSE: 300 mg/day (divided over two doses)^{6,26}

b) nefazodone DOSE: 450 mg/day (divided over two doses)^{6,26}

c) mirtazapine DOSE: 30mg nightly.²⁶

d) fluoxetine DOSE: 20–40 mg daily.^{6,51}

4. Anticonvulsants and mood stabilizers

Ex: Gabapentin.^{7,51}

Lithium carbonate DOSE: 600 to 900 mg/day.^{6,51}

divalproex DOSE: 1500-2000mg/day (divided over two doses)^{6,7,26,51}

5. anxiolytics ex: Buspirone DOSE: maximum 60 mg/day.^{6,26,51}

6. a2-adrenergic agonists

7. glutamatergic modulator

Ex: N-acetylcysteine DOSE: 1,200 mg twice daily for 4 weeks to 24.^{6,7,51}

8. antipsychotic

Ex: quetiapine DOSE: 200mg/day (divided over two doses)²⁶

9. sedative-hypnotics

Ex: Zolpidem: 12.5mg nightly.^{7,26}

10. opiate antagonist

Ex: naltrexone DOSE: 50mg/day.^{6,26}

11. Dopamine agonists:

Ex: Entacapone DOSE: upto 2000mg/day.⁶

12. Norepinephrine Reuptake Inhibitor-

EX: Atomoxetine DOSE: 25, 40, 80mg/day.⁶

13. γ-aminobutyric acid-B receptor agonist

Ex: Baclofen DOSE: 60 and 90mg (divided over three doses)^{7,26}

Psychotherapeutic Treatments

Psychotherapeutic treatments for CUD primarily focused on cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), contingency management (CM), and the evidence base recommended that a combination of the three treatment modalities produces the best outcomes.^{7,52}

1. Cognitive-Behavioural Therapy

Cognitive-behavioural therapy aids patients to recognize contingencies of using behavior, develop relapse prevention and coping skills, and pursue alternative prosocial behaviors. Techniques include self-monitoring, cognitive restructuring, cost-benefit analysis, role playing, and modeling.^{7,52}

2. Motivational Enhancement Therapy

Motivational enhancement therapy (MET) is based upon motivational interviewing (MI) principles²⁰ and looks for enhancing motivation to change by providing nonjudgmental feedback, exploring and resolving ambivalence, and collaborative goal setting. The analyst make use of an empathic nonconfrontational approach to elicit “change talk” (e.g., “I really need to stop smoking pot before I get into trouble again”), which predicts subsequent behavior change.^{7,52}

3. MET/CBT plus Contingency Management

CM have been studied broadly in substance abuse treatment, frequently as an adjunct to psychotherapy. CM is based upon operant conditioning of a target behavior (e.g., negative urine drug screen, session attendance) and is most effective when reinforcement opportunities are frequent, reinforcers instantly follow target behavior, perceived value of the reinforcer is high (though the actual value may be low), the reinforcement schedule is



escalating (i.e., opportunities for reinforcement increase with successive achievement of target behavior), and failure to meet the reinforcement criterion results in resetting of the reinforcement schedule.^{7,52}

4. Alternate Approaches

Though the major part of clinical trials for CUD have been examining CBT, MET, and CM, alternate approaches have also been studied. Multifaceted family therapy (MDFT) is a family-based treatment that has been shown promising results, particularly with adolescents. MDFT involves at least one caregiver and focuses on four interdependent treatment domains: the adolescent domain, the parent domain, the interactional domain, and the extrafamilial domain.^{7,52}

CONCLUSION

During the past decade, marijuana use disorders have increased in all age groups. In the midst of the political and Social debate about marijuana and its recreational and medicinal uses, Science is trying to elucidate the risks of a substance subject to contrasting judgments. The main active substance in the cannabis plant is D9-tetrahydrocannabinol (THC) with some contribution from other cannabinoids. In some regular but massive user's cannabis causes drug dependency and is associated with psychoses and prolonged changes in mental health. Cannabis addiction is the major complication in the world including India. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as pregnant women and adolescents. Physiological Counselling has very important role in de-addiction. Paralleling the rise in marijuana use disorders, treatment admissions for primary marijuana dependence have increased both in absolute numbers. Behavioral treatments, such as motivational enhancement therapy (MET), cognitive-behavioral therapy (CBT), and contingency management (CM), as well as family-based treatments have been carefully evaluated. The extent of marijuana use and its associated consequences clearly indicate a public health problem that requires systematic effort focused on prevention and intervention.

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