

Cannabis and psychopathology: The meandering journey of the last decade

Abhishek Ghosh, Debasish Basu

Department of Psychiatry, Drug De-addiction and Treatment Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Since its inception cannabis has been observed to be associated with various psycho-pathology. In this paper, the authors have reviewed the advancement made in this area over the last decade. The association between cannabis and schizophrenia has been researched more intensively. The controversy regarding the reliability, clinical utility, and the existence of a cannabis withdrawal syndrome has also been settled. Recent studies also buttressed the possibility of acute and chronic effect of cannabis on various cognitive functions. There has been a plethora of research regarding the treatment for cannabis use disorders. But the new and most interesting area of research is concentrated on the endocannabinoid system and its contribution in various psychiatric disorders.

Key words: Affect, cannabis, cognition, endocannabinoid, schizophrenia, treatment, withdrawal

INTRODUCTION

The use of cannabis has been known to mankind for time immemorial. As per the latest World Drug Report released by United Nations Office on Drug and Crime in June 2014, the global market for cannabis (both herb and resin) continues to expand, with two-third of the reporting countries ranking cannabis as the primary substance of abuse.^[1] In 2012, between 125 million and 227 million, people were estimated to have used cannabis, corresponding to between 2.7% and 4.9% of the population aged 15–64 years. There is a trend of increasing use of cannabis in America, Oceania, and several Asian countries.^[1] Data from the National Household Survey in India demonstrated a prevalence figure of 4% and 3.3% for lifetime and current cannabis users.^[2] Cannabis once thought to be a “harmless” to even as a medicinal herb, now has a cumulative evidence for its potentially damaging consequences. It has been linked to a plethora of psychopathology, cognitive dysfunction, and other psycho-social adversities. Interestingly, in recent times,

especially after the discovery of endocannabinoids (eCB) system, there has been a renewed attention for the use of cannabis derivatives for therapeutic purpose.

In the year 1994, a paper titled “Cannabis-related psychiatric syndrome: A selective review” was published in this journal.^[3] The area was revisited in 2004,^[4] after a period of 10 years. Now, after yet another decade, there has been a perceived necessity to have a re-look on the entire conundrum of cannabis and related disorders. It would be useful, in fact, imperative to carry this review forward from the previous one, published in 2004. In their concluding remarks, the authors acknowledged that though there has not been any earth-shattering research in the area of cannabis, there were several large-scaled well-controlled epidemiological studies which had the potential to accept, reject or to modify the existing literature. Apart from the ever baffling phenomenon of cannabis and schizophrenia, authors had recognized several other areas of controversy, starting from cannabis withdrawal to cannabis-related cognitive impairment, eventually opening up an opportunity

Address for correspondence: Dr. Debasish Basu,
Department of Psychiatry, Drug De-addiction and Treatment
Centre, Postgraduate Institute of Medical Education and
Research, Chandigarh - 160 012, India.
E-mail: db_sm2002@yahoo.com

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to explore the enigma. In the last decade, there has been some clarification in many of these areas; there is emerging interest in some new areas; waning of interest in other few areas; and a few replication researches to substantiate the existing knowledge. The PubMed search word “cannabis” generated 5820 results during this period (2004–2013) as compared to 1879 from 1994 to 2003 and 871 from 1984 to 1993. These numbers signify an ever growing enthusiasm in cannabis research. Not only in terms of number of publications, the global community has responded to the increasing concern of cannabis use by various conferences like recently an “International Scientific Conference on Cannabis and Health” has been announced by the European Union.

Though there has been a controversy regarding cannabis policy owing to the scuffle between the liberal and the conservative lobbies, this area has been consciously overlooked in this review because the author’s thought this to be beyond the purview of this article.

DATA SEARCH METHODOLOGY

The data search strategies used included electronic databases as well as hand-search of relevant publications or cross-references. The electronic search included PubMed, Google Scholar, PsychINFO, Scopus, and Ovid. Cross-searches of electronic and hand search key references yielded other relevant material. The search terms used in various combinations were cannabis, schizophrenia, cannabis withdrawal, eCB, cannabis and cognition, treatment, drugs, cannabis and India. We have purposely chosen to remain silent about the association between the externalizing psychopathology in the children and adolescent and cannabis use because we have planned to review cannabis and concurrent adult psychopathology. The data inclusion for this review was guided by the following principles. We included studies published after 2003 till December, 2013. As we intended for a narrative review, we were over-inclusive and did not restrict our data inclusion by any standardized methodology. The intent was to include as much research and as many aspects as possible. Wherever applicable, the strengths and the limitations of the cited research are also discussed. The search methodology was similar to the previous two reviews to ensure comparability and consistency. The results are discussed under two broad sections: Research to clarify confusion (which deals in the areas of past active research, with new findings over the last decade or so), and research in new domains (dealing in research frontiers that have come up actively in the past decade).

RESEARCH TO CLARIFY CONFUSION

Cannabis and schizophrenia

It is well-known that regular cannabis use and psychotic disorders like schizophrenia are associated in the general

population^[5,6] and heavy cannabis users are over-represented among new cases of schizophrenia.^[7] The previous review suggested that “cannabis use might be causally related to development of schizophrenia in an indirect way, but its use may precipitate disorders in persons who are vulnerable for developing psychosis and worsen the course of the disorder among those who have already developed it.” The usual confusion in this association is due to the presence of various confounding factors which can be common to both cannabis and schizophrenia. Subsequent studies endeavored to settle the confusion.

There were at least seven large-scale, prospective, population-based studies chiefly from various European countries.^[8–14] Three of these studies found that even after controlling for the effect of confounding variables the association of cannabis and Schizophrenia remained significant, though the strength of association decreased. There are no < 2 meta-analyses examining the association between cannabis and Schizophrenia. Moore *et al.*^[15] reported an increased risk (odds ratio = 1.4) of any psychotic outcome in individuals who had ever used cannabis. Findings were indicative of dose-response relationship of cannabis and Schizophrenia. This meta-analysis had only included studies which had adjusted for all possible confounding variables such as other substance use, personality traits, sociodemographic characteristics, intellectual functioning, and other mental health problems. To reduce or eliminate the effect further, McGrath *et al.*^[16] conducted a sibling pair analysis and found that the risk of nonaffective psychosis increases by 2 times following exposure to cannabis as young age. Another recent meta-analysis found that the age of onset of psychosis is about 2.7 years earlier in the cannabis user as compared to alcohol user.^[17] The same finding was replicated in another study which adjusted the potential confounding factors.^[18] Hence, from these findings, it is quite evident that there has been a direct association of both these conditions.

Next obvious question would be whether this association is causal? For the causality, association should be consistent, plausible, and specific. The biological plausibility of this association could be understood through the common neurobiological underpinning of these two apparently distinctive conditions. Long-term heavy cannabis use (without schizophrenia) may lead to reduced hippocampal and amygdala volume and also smaller cerebellar white matter. Smaller thalamic volume has also been reported in the heavy cannabis user.^[19,20] These findings are analogous to those found in schizophrenia. But these brain abnormalities are nonspecific and are also found in subjects with other substance use disorders or even psychiatric disorders other than schizophrenia. From the neurotransmitter perspective, dopaminergic hypothesis of schizophrenia postulates that positive symptoms are due to excess dopamine in the meso-limbic pathway. There is some evidence alluding to the disruption of the

eCB system by exogenous cannabis resulting into excess dopaminergic transmission in the meso-limbic tract.^[21] The same eCB disruption by heavy cannabis use has also been implicated in the altered neurogenesis, neuroplasticity, maturation, migration, glia formation. As a result, there would be disordered neurodevelopment which is akin to schizophrenia.^[22] Electroencephalographic finding of cannabis use disorder, and Schizophrenia is also observed to be comparable.^[23] Decreased theta coherence is strongly associated with positive psychotic symptoms and also cannabis use. All these biological evidence to explain the association of cannabis and schizophrenia are speculative and need further replication.

Only a small fraction of people who use cannabis develop schizophrenia. This inconsistency points toward the possibility of the inherent vulnerability in this small portion of the population. Genetic susceptibility has been investigated in the last decade. The first evidence of such gene-environment interaction has been demonstrated by Caspi *et al.*^[24] who identified a functional polymorphism in the Catechol-O-methyltransferase gene which has low enzyme activity. The *val* homozygous allelic variant has low enzyme activity resulting into impaired degradation of monoamines and increased the level of dopamine which is implicated in the development of schizophrenia. It has been seen that people who are homozygous to *val* allele have 10 times higher risk of developing schizophrenia than those who have *met* allele. But the result of this study has not been replicated in another research.^[25] While many genes have been implicated, a sibling analysis and proband follow-up study conducted by van Winkel and the Genetic Risk and Outcome of Psychosis Investigators examined interactions between cannabis use and 152 single nucleotide polymorphisms in 42 candidate genes.^[26] The finding suggested that the variation in the AKT1 single nucleotide polymorphism may mediate both short-term as well as longer-term effects on psychosis expression associated with the use of cannabis. Dopamine (D2) receptor function has been mediated by AKT1, which is a serine-threonine kinase and acts through Glycogen synthase kinase 3 pathway. Overall, the evidence toward specific genetic vulnerability is inconclusive, and more research is warranted in this area to either accept or refute the existing knowledge.

There are some environmental factors which are postulated to mediate the effect of cannabis and influence the outcome. The presence of both childhood sexual trauma and cannabis use increases the risk of psychotic outcome.^[27,28] This was recently replicated in the analysis of prospective data from two independent population-based studies.^[29] Urban upbringing is another social variable which also been brought into attention for increasing vulnerability toward the “psychotogenic” effect of cannabis.^[30-32] Like The biological explanation, this association is speculative and

mostly indicative of cross-sensitization which is likely to be mediated by dopamine.^[33]

Though strong and conclusive evidence is yet to come, these genetic and environmental factors are expected to play a critical role in the progression of cannabis use to schizophrenia. Current consensus is that cannabis is neither necessary nor sufficient to cause schizophrenia. It is considered as a component cause for schizophrenia, including other environmental and genetic factors. Early and heavy use of cannabis compounded the risk further.^[34] Panel 1 portrays the essential aspects of cannabis and schizophrenia research.

Cannabis and other major psychiatric disorders

Another major question regarding the impact of adolescent cannabis relates to its role in negative affective disorders, like major depressive disorder, which are increasingly burdensome worldwide. Longitudinal studies reporting an association between cannabis uses and developing depression provide mixed results. In a recent meta-analysis, 57 studies were included for full-text review, of which 14 were included in the quantitative analysis (total number of subjects = 76,058). The odds ratio for developing depression in cannabis users compared with controls was 1.17. The odds ratio for heavy cannabis users developing depression was higher (1.62), compared with nonusers or light users. Meta-regression revealed no significant differences in effect based on age of subjects and the marginal difference in effect based on length of follow-up in the individual studies.^[35] There was large heterogeneity in the number and type of control variables in the different studies. Early cannabis use in the teens is also associated with increased suicidal ideation and attempts in the early adulthood.^[36] Importantly, accumulating evidence also implies that both adolescent exposure and the continued use during adulthood are required for these associations suggesting that the disease may be mitigated with cannabis cessation.^[37,38]

Panel 1: Cannabis and schizophrenia

What was already known before the last decade?

Use of cannabis is associated with the onset and the poor prognosis schizophrenia

Early, heavy and prolonged use increase the risk

What has been added/clarified during the last decade?

Even after consideration for the confounding variables the association of cannabis and Schizophrenia remains significant

Biological plausibility of such association has been studied

Studies allude to the possibility of gene-environment interaction:

Cannabis and COMT gene functional polymorphism

Some environmental factors mediate the effect of cannabis increasing vulnerability for schizophrenia

Cannabis is considered as a “component cause” for Schizophrenia: It is neither sufficient nor necessary to cause schizophrenia

What remains unanswered?

Evidence toward specific genetic vulnerability is inconclusive: Lack of consistent and replicated results

Role of e-CB system for the development of schizophrenia

e-CB – Endo-cannabinoid; COMT – Catechol-O-methyltransferase

Future longitudinal studies are clearly still needed to examine the contribution of the developmental period of onset and cessation of cannabis to the risk of negative affect. In addition, *in vivo* neuroimaging in humans can also offer much-needed neurobiological insights. Evidence already exists demonstrating volumetric impairments in the amygdala, a brain region central to affective and addictive disorders, in cannabis users during early^[39] and late^[40] adolescence. Similarly, structural changes in the hippocampus, which is linked to depression,^[41] have been reported in individuals with cannabis use during late adolescence.^[42]

In the recent years, several animal studies have been conducted to explore about the negative affectivity following exposure to cannabis. Exposure to tetrahydrocannabinol (THC) in adolescent and especially female mice causes depression-like behavior in the forced swim test and sucrose preference test.^[43,44] Findings suggest that adolescent cannabinoid exposure could affect the liability to mood disorders later in life, and the potential gender differences may relate in those well-documented in depression. Altered anxiety-like behavior as a consequence of adolescent cannabinoid exposure is apparent in experimental animals though the relationship is not straightforward. Anxiogenesis or anxiolysis has been reported depending on the period of cannabinoid exposure and the specific task used to model anxiety. For example, chronic exposure to cannabinoid agonists – such as THC during mid-to late-adolescence, increases social anxiety as measured with a social recognition task. Other measurements of stress that do not rely on social interaction, such as the open-field and elevated plus-maze tests, indicate varying degrees of anxiolysis, not anxiogenesis.^[45-47] These anxiolytic effects were observed after mid-to late-adolescent exposure, whereas earlier, prepubertal exposures were anxiogenic.^[48,49]

Panel 2 depicts the salient points with regard to cannabis and other major psychiatric disorders.

Panel 2: Cannabis and other major psychiatric disorder

What was already known before the last decade?

Association between depression and cannabis use

Role of shared environmental and genetic factors explaining the association

What has been added/clarified during the last decade?

Association between major depressive episode and cannabis use substantiated in longitudinal studies

Early and prolonged use of cannabis is the predisposing factor for the development of a depressive episode

Association between adolescent cannabis use and adult suicidality

Various animal research to fill gaps of knowledge regarding the direct link between early life cannabis use and negative affect

What remains unanswered?

Effect of cannabis in the developing brain to explain associated

MDD/anxiety disorder

Cannabis: Anxiolytic versus anxiogenic

MDD – Major depressive disorder

Cannabis withdrawal syndrome

There has always been skepticism, whether cannabis can produce physiological dependence or withdrawal syndrome or even if it can, whether the syndrome is clinically significant enough to warrant a diagnosis. As a result of inconsistent or rather inadequate evidence, cannabis withdrawal syndrome (CWS) is not formally recognized in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV).^[50] The diagnosis is listed, albeit without diagnostic criteria, in the International Statistical Classification of Diseases and Related Health Problems, tenth revision.^[51] Even after the publication of DSM IV-Text Revision, the confusion continued. In a review published in 2002, following pitfalls were pointed out in the existing literature. This review cited (1) the lack of controlled studies, (2) absence of definitions of withdrawal, (3) poor ecological validity, (4) failure to document severity of symptoms, and (5) inconsistent onset and offset of symptoms as the lacunae in research.^[52]

There are some human experimental and animal researches on this area after the review by Smith^[52] has been published. Three rigorous outpatient studies have been reported. These comprehensive prospective studies provided with adequate baseline data demonstrated clinically significant symptoms and a clear delineation of the time course of withdrawal. The results of these four controlled outpatient studies are remarkably consistent and provide validity for a cannabis abstinence/withdrawal syndrome. The generalizability of these studies is limited because the inclusion of only daily users likely produced more severe symptoms than if the light or nondaily users were studied. On the other hand, all four studies excluded treatment seekers, persons with significant psychiatric disorder, and persons who used other substances or abused alcohol. Exclusion of such participants likely resulted in less severe withdrawal symptoms than might have been observed if such participants were included. In addition to human subjects, discovery of the endogenous cannabinoid system, identification of cannabinoid receptors (CB1), and synthesis of a cannabinoid antagonist (SR141716A) made it possible to test for cannabinoid withdrawal in animals using a precipitated withdrawal paradigm. A review of this literature indicated that across multiple nonhuman species, the administration of SR141716A induced clear behavioral signs of precipitated withdrawal. In addition, the specific CB1 site for the action of this withdrawal effect has been determined by using CB1-knockout mice.^[53] These animal studies provide the biological plausibility of cannabis withdrawal. The concern regarding the reliability of CWS has also been addressed. Regarding cross-study reliability, the most consistently reported symptoms are anxiety, decreased appetite/weight loss, irritability, restlessness, sleep problems, and strange dreams. These symptoms were associated with abstinence in at least 70% of the studies in which they were measured. The common symptoms of

cannabis withdrawal are primarily emotional and behavioral and do not typically cause significant physical, medical, or psychiatric disorders. However, this pattern does not mean that cannabis withdrawal is clinically unimportant. Other substance withdrawal syndromes (cocaine, nicotine) were included in the DSM in large part because of acknowledgment that behavioral and emotional withdrawal symptoms are as important, if not more important, than physical symptoms in undermining abstinence. To provide evidence on the clinical significance of CWS, observers suggested that symptoms are quite disruptive to daily living, making cessation difficult and comparable in terms of severity of tobacco withdrawal.^[54,55] A recent study found out cannabis withdrawal is clinically significant because it is associated with functional impairment to normal daily activities, as well as relapse to cannabis use. Sample size in the relapse group was small, and the use of a nontreatment seeking population requires findings to be replicated in clinical samples.^[56] Overall, two extensive reviews on this area published in 2004 and 2006 and subsequent published studies of cannabis withdrawal substantiated the existence, biological plausibility, reliability, and clinical utility of CWS and finally, it has been formally included in DSM 5.^[57-61]

The DSM-5 differs somewhat from several prior proposed diagnostic criteria for CWS.^[62-64] These proposals varied in the content and length of the symptom list and the required number of symptoms. Chung *et al.*,^[64] provided a list of 22 symptoms whereas Budney and Hughes,^[62] proposed a list of 11 symptoms. DSM 5 resorted to seven symptoms drawing them from both the lists. The controversy is also about the threshold for diagnosis of CWS. While one study showed good concurrent and predictive validity for ≥ 4 symptoms, another study demonstrated ≥ 2 symptoms to be clinically significant. DSM 5 opted for a midway between the two and decided its threshold as ≥ 3 symptoms. A recent study evaluated the diagnostic criteria and findings supported predictive and concurrent validity of the same.^[64] But the same study suggested that the list of withdrawal symptoms and number required for diagnosis warrant further evaluation. Panel 3 indicates the striking points for CWS.

Cannabis and cognitive impairment

A large body of literature has accumulated over the last decade examining the effect of cannabis on cognitive performance and eventual functioning. The putative effect of cannabis on cognition is mediated by the CB1 (especially CB1) in the brain areas known to be associated with memory, attention, and other cognitive function. Discovery of the eCB system generated a new interest in this area.

Cognitive function can be affected by either acute or chronic use of cannabis. For demonstrating the acute effect of cannabis, studies have been conducted in both clinical and experimental population. Literature suggest that acute cannabis dose dependently, produces an adverse effect

Panel 3: Cannabis withdrawal syndrome

What was already known before the last decade?

Questionable validity and existence of cannabis withdrawal syndrome
Not included in the DSM IV-TR as a diagnostic category

What has been added/clarified during the last decade?

Animal models to simulate cannabis withdrawal: CB1 knockout mice or specific CB1 antagonist

Human controlled and clinical trials: Remarkably consistent and clinically significant withdrawal symptoms

Definition of standard withdrawal syndrome

Cannabis withdrawal syndrome: Recognized in the DSM 5

What remains unanswered?

Threshold for diagnosis of cannabis withdrawal syndrome

DSM IV-TR – Diagnostic and statistical manual of mental disorders IV-text revised; CB1 – Cannabinoid receptor 1

on a number of cognitive domains. Effects have been consistently observed on short-term memory, particularly immediate memory and recall and retrieval following a lapse of time. Cannabis also affects the ability to learn new information and sustained or divided attention. Cannabis intoxication influences the subjective perception of time too. Experimental studies have shown that cannabis can adversely impact decision making and executive function, though the results are not consistent.^[65] Chronic cannabis use is also associated with impairment in various cognitive domains. A recent study had demonstrated the detrimental effect on prospective memory ability in young adults using cannabis for a long time.^[66] But the subjects were not aware of their deficits. Many other studies additionally revealed effect on basic oculomotor control after chronic cannabis use.^[67] Regular cannabis user's performance on an auditory selective attention task was found to be significantly worse than the normal control. A few studies demonstrated significant deficits such as increased perseveration, decreased verbal learning and memory, and deficits in complex reaction and complex reasoning.^[68,69] Early age of initiation of cannabis use and the prolong duration of use increases the possibility of such impairments.^[70] Chronic effect of cannabis in cognition is difficult to study because of methodological problems like effect of other confounding variables, possibility of preexisting cognitive impairment.

Next important question is whether the cognitive deficits are permanent? Available evidence has been inconsistent in this regard. Some studies have reported complete recovery of impairments even after 4 weeks of abstinence, whereas other studies describe persisting cognitive deficits in attention, memory, and executive function.^[71] One study suggests partial recovery.^[72] In a meta-analysis, residual impairment in verbal memory has most consistently been demonstrated.^[73]

The most intriguing question still remains. Whether there has been any functional significance of these cognitive deficits? The impact of cannabis intoxication on driving

performance in real life setting is difficult and often impossible to determine. Studies using driving simulators and road tests have produced mixed results. Overall, driving skills and behavioral deficits have been encountered in close temporal proximity with cannabis ingestion and these are dose dependent. Combination of cannabis and alcohol which is a common pattern of use in the youth and young adult population clearly increases the risk of unsafe driving.^[74-76] In addition, cannabis has also been linked to low-grade point average, decreased academic satisfaction, poor overall performance in school, and absenteeism. But studies statistically controlled for the confounding variables produced mixed results.^[77] Panel 4 suggests the relevant points regarding cannabis and cognitive impairment.

NEW DOMAINS OF RESEARCH

Treatment for cannabis dependence/use disorders

In the last decade, there has been significant interest in cannabis treatment related research. The amount of pharmacological treatment research overshadows the research in psycho-social intervention. Because of the understanding and acceptability of the existence, clinical importance, and reliability of cannabis withdrawal, treatment directed against withdrawal provides a new thrust in research.

Cannabis withdrawal symptoms are largely nonspecific and mostly begin during the 1st week of abstinence and resolve after a few weeks. Because symptoms of cannabis withdrawal may serve as negative reinforcement for relapse to cannabis use in individuals trying to abstain, pharmacological treatment aimed at alleviating cannabis withdrawal might prevent relapse and reduce. Approaches to treat cannabis withdrawal can be classified into two broad groups: Treating withdrawal with agonist or treating by modulation of the neurotransmitter responsible for the symptoms. There were three published randomized trials on efficacy of dronabinol, which is a CB1 agonist. All these studies are in experimental subjects. Findings suggest that dronabinol is efficacious in ameliorating withdrawal symptoms. The dose range was variable, and sample size was very small except one study. Hence, the results are difficult to generalize.

Panel 4: Cannabis and cognitive impairment

What was already known before the last decade?

Cannabis use is possibly associated with transient cognitive impairment

What has been added/clarified during the last decade?

Acute effect: Dose-dependent; affecting primarily memory and attention

Chronic effect: Mediated by early age of initiation and prolonged use; involving memory, executive function

What remains unanswered?

Nature and type of cognitive impairment: Preexisting or cannabis-induced and effect of other confounding variables

Reversibility of the cognitive impairment: Results inconsistent

Functional impact of such impairment: Mixed evidence and role of confounders

Divalproex, nefazodone, and bupropion were also tried in randomized trials, even in a clinical sample. The results were mostly negative.^[78-81]

Management of cannabis dependence aims at maintaining abstinence or through “harm reduction.” Ongoing research is evaluating 3 major strategies for treatment: Agonist substitution, antagonist, and modulation of other neurotransmitter systems. Agonist substitution has been accomplished with dronabinol. There has been one randomized controlled trial (RCT) with dronabinol which did not improve abstinence but improved treatment retention. Neuromodulation has been carried out by various psychotropics. There were two RCTs of buspirone and fluoxetine each. Though the effect of buspirone is somewhat encouraging in reducing craving and improving abstinence, the effect of fluoxetine has been inconsistent. Naltrexone has also been tried in double-blind-RCTs with negative results. In an open-label trial, baclofen was observed to be effective for maintaining abstinence. N-acetyl cysteine is another medication which was used in another open-label study. Though there was a reduction in the self-reported use, urine cannabinoid levels did not replicate the subjective reporting. As an antagonist approach, rimonabant has been tried in a double-blind parallel group study and found to have a transient effect. Overall, neither a specific approach nor any particular medication has any unequivocal evidence. Duration of treatment is not well-defined. Even studies which have shown some positive results, generalization of those are limited by inadequate statistical power. Most of the studies have included psychosocial management in conjunction with pharmacotherapy. Hence, the relative contribution of each of these approaches is difficult to ascertain.^[82-94]

Various psychosocial interventions have been researched in the last decade. Perhaps, motivation enhancement therapy (MET) and contingency management (CM) were mostly investigated. For MET, number of sessions ranged from 2 to 4, and it is found to be effective in both short and mid-term (3–6 months) in reducing the use of cannabis. Randomized trials showed increased abstinence rate when CM is added to other psycho-social interventions like MET or cognitive behavior therapy.^[95-97] Sample size for these psycho-social interventions was reasonably large, and evidence is also consistent. But further replication is required. Panel 5 refers to the salient points on the management of cannabis use disorders.

Endo-cannabinoid system

Electronic search in the PubMed database with the search word “Endocannabinoids” yielded 186 results over the last decade as compared to the 50 results from 1993 to 2003. This figure itself indicates recent interest on this area. The eCB system modulates the neurotransmission at inhibitory

and excitatory synapses in brain regions relevant to the regulation of pain, emotion, motivation, and cognition.^[98-102] In the last decades, investigation of the eCB system had considerably increased, and our understanding of this system has achieved remarkable aims.^[103] Endocannabinoids, the endogenous ligands, are polyunsaturated fatty acid derivatives that bind to CB1. Specifically, the two most common investigated endocannabinoids are the anandamide and the 2-arachidonoylglycerol which is synthesized “on demand” by the cell membrane in a tissue-specific manner, having prompt agonistic effects on the CB1 via., autocrine or paracrine mediated pathways. These eCB are released from the postsynaptic cell on demand in response to increase of intracellular calcium (Ca^{2+}). Triggered by either depolarization or activation of metabotropic glutamate receptors, and finally acting on the presynaptic terminals as a “retrograde messengers.” The releasing mechanism is through an unknown mechanism. Therefore, endocannabinoids include many different types which are synthesized on demand, are not stored in vesicles; are not released from presynaptic terminals, and are not specific.^[104] Two types of CB1 have been characterized to date: CB1 and CB2 receptors, both metabotropic receptors coupled to $\text{G}\alpha\text{i/o}$ proteins. Though CB1 receptors are located ubiquitously throughout the brain, CB2 receptors, which were once thought to be located in the extra brain areas, are now known to be present in different brain regions under normal physiologic conditions.^[105,106] The role of eCB system in various psychiatric disorders has been investigated. Disequilibrium or malfunctioning of the eCB system might contribute to the etiology of anxiety-related disorders,^[104,107] whereas the pharmacological enhancement of e-CB activation may provide a promising therapeutic tool for the management of such disorders.^[107] Given the successful results accomplished in animal studies, great expectations exist for the future clinical exploitation of this system. As for anxiety disorders, a dysfunction of the eCB system has been proposed to be in the bases of depression.^[109-111] Enhancing the levels of eCBs by inhibiting their deactivation has become a promising antidepressant strategy.^[108,112] In contrast, inactivation of CB1Rs can have detrimental consequences provoking depressive-like symptoms. In fact, rimonabant adverse effects included not only increased anxiety, but also depression and suicidal ideations.^[113-116] For Schizophrenia, there has been accumulating evidence from the animal research. In spite of the current discrepancies regarding CB1R changes in animal models of schizophrenia, present findings point to the eCB system as a pivotal neuromodulatory pathway that may have a critical relevance in the psychotic-related behaviors observed in these animals, that is, altered emotionality and social and cognitive deficits.^[117]

The distinctive role of cannabidiol (CBD) has also been examined. CBD is the main nonpsychotropic phyto cannabinoid found in the *Cannabis sativa* plant, constituting up to 40% of its

extract. Recent comprehensive reviews indicate that CBD is one of the most promising candidates for therapeutic use in a wide range of disorders, including neuropsychiatric.^[118-120] Leweke *et al.*^[120] found that CBD significantly reduced psychotic symptoms in acute schizophrenia with potency similar to amisulpride but with fewer side effects such as extrapyramidal symptoms, increase in prolactin, and weight gain. The mechanism of its antipsychotic action is still elusive. Panel 6 alludes to the summary of eCB system in psychiatry.

Though there are fleeting reviews on amotivation syndrome,^[121] overall the interest has waned off in this domain. Even a recent paper on this area concluded “cannabis does not impair motivation. Its impact on subjective well-being is small and may actually reflect lower well-being due to medical symptoms rather than actual consumption of the plant.”^[122] Cannabis psychosis, another area which had gained special attention in the previous decades, has been ignored largely of late. Acknowledging the same, a recent review failed to find out any distinctive psychopathology in cannabis psychosis as compared to the other forms of psychosis. However, they were guarded in their interpretation and had proposed further research in this area to make conclusive remarks on the existence and validity of cannabis psychosis.^[123] Cannabis-induced flashback is the other area which has been seldom discussed in the last decade.

Panel 5: Treatment for cannabis dependence/use disorders

What was already known before the last decade?

Minimal treatment-related research prior to the last decade

What has been added/clarified during the last decade?

Cannabis withdrawal: Dronabinol in experimental subjects

Cannabis dependence: Buspirone has some evidence; fluoxetine, N-acetyl cysteine, dronabinol, and rimonabant have been tried without much benefit
Psychosocial treatment like motivation enhancement, cognitive behavior therapy, and contingency management is the mainstay of treatment for cannabis dependence

What remains unanswered?

Type and duration of long-term pharmaco-prophylaxis for the maintenance of abstinence

Panel 6: e-CB system

What was already known before the last decade?

Existence of e-CB system: e-CBs are produced on demand in the postsynaptic membrane and are retrograde messengers
e-CB acts primarily on CB1 receptor

What has been added/clarified during the last decade?

Role of e-CB in various psychiatric disorders

Blockage of CB1 receptor/decrease in the e-CB may result in depression and anxiety like symptoms

e-CB also implicated in schizophrenia: At least in the animal models

Possibility of therapeutic role of CBD in psychosis

What remains unanswered?

Exact mechanism of e-CB in the pathogenesis of various neuropsychiatric disorders

Therapeutic effect of e-CB

e-CB – Endo-cannabinoid; CB1 – Cannabinoid receptor 1; CBD – Cannabidiol

Indian research

There has been only a handful of research on cannabis from India in the last decade. One study attempted to research the clinical presentation of cannabis-related psychosis and effect of abstinence. 22 consecutive male subjects were recruited for the purpose of the study, and they were followed-up in a controlled environment for the next 7 days. Assessment was done with Brief Psychiatric Rating Scale. Results demonstrated that the cannabis-related psychosis presented with a predominantly affective psychosis and prominent thought disorder, excitement, and violence. All subjects showed improvement in symptoms with abstinence from cannabis.^[124] Another study aimed to understand the influence of cannabis on cerebral glucose metabolism in certain predetermined regions of interest. 2-fluoro, 2-deoxy-glucose–positron emission tomography (FDG–PET) has been carried out in 16 cannabis-dependent subjects who had recently consumed cannabis and an equal number of noncannabis using volunteers. The two groups differed in their lateral and medial temporal glucose uptakes by approximately 16–24%. Significant differences in inter-regional correlations in the medial temporo-frontal and parieto-thalamic were noted between the two groups. These results suggested that at least a part of the cortico-subcortical relationship is altered among cannabis users.^[125] A similar study by the same group of researchers using FDG-PET purported to understand the patterns of glucose uptake in important brain regions among individuals with cannabis dependence and schizophrenia. Significant differences were noted among individuals with cannabis dependence and schizophrenia in the medial and lateral temporal regions. Study findings suggested that cannabis dependence can alter interregional relationships in a manner similar to schizophrenia.^[126]

CONCLUSION

In the last 10 years, in addition to the usual clinical and phenomenological research, there has been an upsurge of biological research in cannabis. By and large, it is in concordance with the research interest in addiction. Nevertheless, the discovery of e-CB system as a neuromodulator has opened up an opportunity for additional research for the understanding of neurobiology and treatment of various psychiatric and addictive disorders. The existence, validity, reliability, and clinical importance of cannabis withdrawal have been acknowledged, and it has found a place in the current psychiatric nosology. The association of cannabis and Schizophrenia has been studied further. There has been better-controlled longitudinal research, including meta-analysis to explore the baffling association. Current consensus alludes to the possibility of “component causality.” There has also been some research to find out the genetic vulnerability for the development of Schizophrenia following cannabis use. Cannabis and cognitive impairment has been investigated further. Though there is unequivocal evidence of acute and chronic effect of cannabis in cognitive function and the domains of cognition

affected, evidence for the reversibility of these dysfunctions is mixed. Moreover, the effect of such cognitive impairment in functionality is also a matter of controversy. Though there are various treatment-related researches, the evidence for drug treatment to maintain cannabis abstinence is still preliminary and inconclusive.

Overall, the journey of cannabis research in the last decade was innovative enough to excite the scientific community, conclusive enough at least in some areas to settle down controversy and still uncertain enough in few domains to keep the quest for answers alive.

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