REVIEW ARTICLE

Cannabis and psychopathology: 2024 Snapshot of a meandering journey

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ABSTRACT

Background: Cannabis has been associated with psychopathology since ancient times, but controversies continue despite important advances in the field. This article is the fourth one in our decadal series of review articles that have been providing an update snapshot of the meandering journey of the research findings in this area.
Aims: This narrative review of a comprehensive literature search over the past 10 years aims to provide an update and current understanding, while raising unanswered questions for the future, focusing on the following areas: (a) nosological changes in cannabis-related psychiatric syndromes; (b) psychopathology associated with the newer category of synthetic cannabinoids; (c) cannabis withdrawal syndrome); (d) cannabis and psychosis; (e) cannabis and mood disorders; (f) cannabis and suicidality; (g) prenatal cannabis use and psychopathology in the offspring; (h) effect of recent liberal policy overhaul on cannabis control in certain countries/areas on psychopathology and adverse outcomes; (i) cannabis and cognition; and (j) cannabis, psychopathology, and genetics.
Methods: The data search strategies involved a combination of electronic databases and manual hand-searching of relevant publications and cross-references using selected search terms. The primary electronic search focused on Medline and PubMed Central databases but extended to databases such as Google Scholar, PsychINFO, Scopus, and Ovid for specific sections. Key references identified through electronic and manual searches provided additional material. Inclusion criteria for the review spanned studies published between January 2014 and June 2024, with more emphasis placed on recent studies (post-2020) while ensuring historical coverage.
Results: The narrative review aimed to be comprehensive, including a broad range of research without strict methodological exclusions. Strengths and limitations of cited research are discussed when applicable, maintaining consistency with three prior reviews. We focused on psychopathology and psychiatric syndromes, human (rather than animal) studies, and applied (rather than basic) research. We have only focused on policy with reference to psychopathology and not on that entire area because that would be beyond the scope of this article. There are important updates in all the areas covered. There are newer syndromal entities in ICD-11, which also includes synthetic cannabinoids for the first time. Cannabis withdrawal syndrome has been better characterized. The association between cannabis and psychosis has been robustly

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established especially for very high-potency cannabis and for vulnerable populations, particularly young people. Work is in progress elucidating the causal mechanisms. The links between cannabis and mood disorders as well as suicidality and cognitive impairment are better characterized, though questions remain. Recent liberalizing policies on cannabis have produced newer findings on prenatal and accidental cannabis use (with deleterious effects on the offspring) and on later psychopathology (mixed findings, but a documented increase in emergency visits related to recent cannabis use). This is an area which will require active monitoring for new data.

Conclusion: The field of cannabis use and psychopathology continues to collect new data and settle some old controversies while raising new questions, which are important to address in view of the wide use of cannabis worldwide and its implications for public health.

Key words: Cannabis, genetics, mood disorders, policy, prenatal exposure, psychopathology, suicidality

INTRODUCTION

Cannabis and psychopathology have been intertwined in history. Around 22.8 crore people used cannabis in 2022, and cannabis was the most commonly used illicit substance worldwide.[1] Around 2.8% of Indians use cannabis at some point of their life, and around 0.66% of the population have problematic cannabis use.[2] The trend of cannabis use has been increasing worldwide in the past couple of years. Current policy changes, leading to increased access to recreational cannabis use, and a perceived sense of safety might contribute to this trend. Simultaneously, there is increased hospitalization due to cannabis use-related problems and increased prevalence of high-potency cannabis with higher concentration of delta-9-tetrahydrocannabinol (THC), which has a higher magnitude of harm.[1] In this situation, consolidating our knowledge about the psychological effects of cannabis and identifying the lacunae of our knowledge are of utmost importance for a comprehensive service provision to the patients in need as well as for broader public health implications.

The relationship between cannabis and mental illnesses has traditionally been an enigmatic one. The Hemp commission faced the similar issues 130 years back and noted the need "to make an effort to sift and test the evidence". Interestingly, the opinion regarding the relationship was highly colored by subjective belief rather than objective evidence.[3] A similar concern persists and probably got aggravated during this era of information overload. This was highlighted in the first article in this series dating back to 1994, where the authors noted the controversies regarding the relationship of cannabis and psychosis. The subjective bias, difference in theoretical framework, and their effects on cannabis research were also focused.[4] Two more reviews on the same topic at an interval of 1 decade each highlighted the progress of contemporary research on cannabis and psychopathology and psychiatric illnesses. The controversies between cannabis and psychosis gradually settled, and cannabis emerged as an important component cause of psychosis.[5,6] New research areas emerged, such as relationship of cannabis with affective disorders, cognitive impairment, and effect of prenatal cannabis exposures. The snapshots of cannabis-related researches in psychiatry at the interval of another decade will give us a glimpse of the unfolding spectrum of the interplay of cannabis and psychopathology.

While gleaning through the recent literature, there were several areas noted for their clinical and public health salience. These constituted the areas covered in this review.

Thus, this article is the fourth one in our decadal series of review articles that have been providing an update snapshot of the meandering journey of the research findings in this area. This narrative review of a comprehensive literature search over the past 10 years aims to provide an update and current understanding, while raising unanswered questions for the future, focusing on the following areas: (a) nosological changes in cannabis-related psychiatric syndromes; (b) psychopathology associated with the newer category of synthetic cannabinoids; (c) cannabis withdrawal syndrome; (d) cannabis and psychosis; (e) cannabis and mood disorders; (f) cannabis and suicidality; (g) prenatal cannabis use and psychopathology in the offspring; (h) effect of recent liberal policy overhaul on cannabis control in certain countries/areas on psychopathology and adverse outcomes; (i) cannabis and cognition; and (j) cannabis, psychopathology, and genetics. The scope of our review is to elaborate the relationship of cannabis and psychiatric conditions. So, we will deliberately restrict our discussion on this field. There have been a significant body of research on the endocannabinoid system and its role on different physical ailments, but we will not be discussing those issues. Similarly, we will discuss about the policy-related issues only where it is clinically relevant. Please see Figure 1 for an overview of the organization of the article.

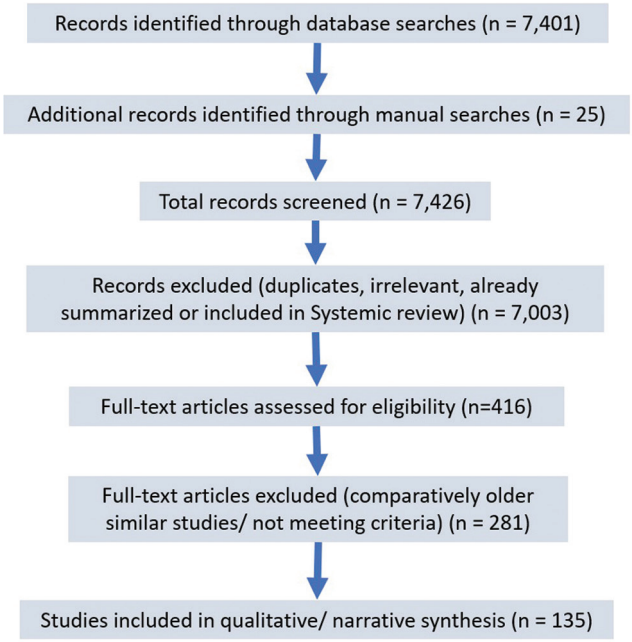

Figure 1: Article flow diagram for included studies

METHODS

Like the third update in the series,[6] this review follows similar methodologies but incorporates more robust search strategies to reflect advancements in the field. We have expanded on prior research questions while addressing newer challenges, such as the impact of high-potency cannabis, the implications of widespread legalization, and prenatal cannabis exposure. The data search strategies involved a combination of electronic databases and manual hand-searching of relevant publications and cross-references. The primary electronic search focused on PubMed but extended to databases such as Google Scholar, PsychINFO, Scopus, and Ovid for specific sections. Key references identified through electronic and manual searches provided additional material.

The PubMed search terms for cannabis use were: ((((Cannabis) OR Cannabis use disorder) OR Cannabis addiction) OR Cannabis use) OR "Marijuana Abuse"[Mesh]). For cannabis withdrawal, terms such as (((("Withdrawal symptoms") OR "Withdrawal Syndrome") OR "Cannabis Withdrawal") were utilized. The cannabis use term was applied in combination with other search terms using the AND Boolean operator. For example:

- **Psychopathology**: ((((("Psychopathology"[Mesh]) OR "Mental Disorders"[Mesh]) OR "Mood Disorders"[Mesh]) OR "Psychotic Disorders"[Mesh]).
- **Cognition**: (((((("Neurocognitive Disorders"[Mesh]) OR "Neurobehavioral Manifestations"[Mesh]) OR "Cognitive Symptom") OR "Cognition") OR "Memory") OR "Attention").
- **Genetics:** "Genetics"[Mesh] OR "Human Genetics"[Mesh] OR "Genetic Linkage"[Mesh] OR "Genome-Wide Association Study"[Mesh] OR "Pharmacogenetics"[Mesh]
- **Suicide**: ((("Self-Injurious Behavior"[Mesh]) OR Suicide) OR Suicidal Behavior) OR Self-harm Behavior.
- **Perinatal cannabis exposure**: (((prenatal OR "during pregnancy") OR antenatal OR pregnancy OR "peri pregnancy") OR perinatal OR preconception OR maternal) AND (offspring OR adolescents OR youths OR young OR child OR infant OR childhood OR "young adults") AND ((((("Attention Deficit Disorder with Hyperactivity" [Mesh]) OR "Autism Spectrum Disorder" [Mesh]) OR "Child Development Disorders, Pervasive" [Mesh]) OR "Neurodevelopmental Disorders" [Mesh])

Inclusion criteria for the review spanned studies published between January 2014 and June 2024, with more emphasis placed on recent studies (post-2020) while ensuring historical coverage. The narrative review aimed to be comprehensive, including a broad range of research without strict methodological exclusions. Strengths and limitations of cited research are discussed when applicable, maintaining consistency with three prior reviews. In addition to the formal search using predefined search strings, additional manual search was also done electronically based upon leads obtained from other studies and from screening for general latest trends.

Boundaries for exclusion were set on topics like medicinal cannabis and policy controversies (unless related to psychopathology), basic science or animal studies (except when relevant to psychopathology), and detailed discussions on cannabis use disorder (CUD) treatment, for which updated reviews can be referred to.[7,8] Please see Figure 2 for the study selection flow.

RESULTS

Current nosological changes of cannabis dependence and related disorders

The World Health Organization (WHO) published the 11th version of International Classification of Diseases (ICD-11) in 2019, 25 years after the release of ICD-10. The conceptualization of substance use disorder, diagnosis, and remission criteria changed significantly in ICD-11. ICD-11 incorporated the disorders due to the use of synthetic cannabinoids separately (6C42). ICD-11 also proposed a defined set of cannabis withdrawal symptoms, which was not recognized in its previous version.[9] Panel 1 summarizes the changes in ICD-11, which are pertinent to cannabis.

Synthetic cannabinoids and psychiatric symptoms

Synthetic cannabinoids (SC) are a group of new psychoactive substances that mimic the physiological effect of δ9 THC on our bodies. Till 2023, more than 100 different types of

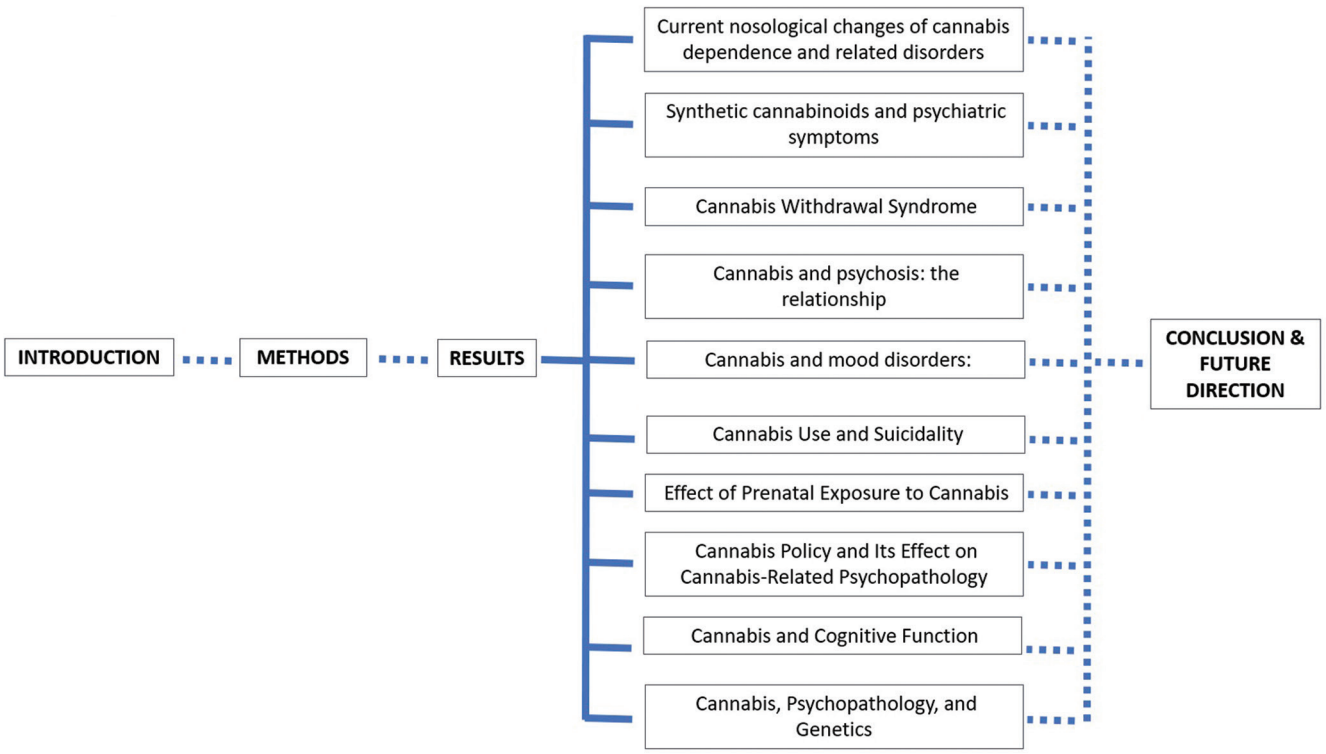

Figure 2: Organization of the article

Panel 1: Highlights of changes in Cannabis dependence and related disorders in ICD-11

General changes, pertinent to cannabis use disorder:

- Introduction of hazardous and single-episode harmful substance use
- The reduction of number of criteria from six to three (i.e., impaired control, salience, physiological features)
- Increased flexibility to diagnose substance-induced psychiatric disorders.
- Remission course specifier – early and sustained; full and partial, which denotes a clear shift from abstinence-oriented model to recovery-oriented model.

Cannabis specific changes:

- Introduction of cannabis withdrawal symptoms.
- Synthetic cannabinoids as a separate diagnostic category.

synthetic cannabinoids were reported from various parts of the globe.[1] Regular emergence of newer molecules, difficulty in detection of molecules in a biological sample, and poor knowledge regarding the epidemiological and clinical aspects of the SCs complicate the assessment and management of cases. One nationally representative sample of US showed that the prevalence of lifetime use of SC was around 10%, and that of more frequent use (six or more times) was around 3% in high-school seniors (8th, 10th, and 12th standard students).[10] One recent multicentric study in India revealed that around 5.3% of substance users seeking treatment from tertiary level hospitals were exposed to synthetic cannabinoids.[11]

How SCs are different from natural cannabinoids (NCs)? Various pharmacological compounds like HU-210, AM-694, and JWH-018 are the active ingredients of synthetic cannabinoids. Many users consider SCs to be a safer alternative than NC. Interestingly, the scientific literature points toward many systemic side effects of SCs. A recent review of case reports and case series on synthetic cannabinoid toxicity revealed that acute SC exposure is associated with cardiovascular, hematological, renal, and neuropsychiatric complications. The major neurological complications are dizziness, drowsiness, delirium, cerebrovascular accidents, and seizure.[12] Most of the SC molecules have several times higher affinity on cannabinoid (CB1) receptor than that of δ9 THC, along with action on dopaminergic, serotonergic, and glutamatergic systems.[13] High-potency SC molecules are associated with a higher frequency of associated seizures and status epilepticus, which may be up to 14–15% of the population, seeking treatment for SC intoxication.[14]

Does the higher potency translate into higher susceptibility to developing psychotic symptoms? A multinational study attempted to compare the psychotogenic effects of synthetic (SC) and natural (NC) cannabinoids. The researchers compared 238 SC users with 129 NC users. The SC users had higher scores in the severity of substance use disorder, mood symptoms, and psychopathology. One of the limitations is the comorbid use of other substances and the overlap of NC use in the SC group, but the recent use of NC was present only in around one in five participants.[15]

Nature of psychosis with SC: phenomenology and psychopathology: Another systematic review assessed 13 studies across Europe, America, and the Western Pacific and four studies worldwide. The qualitative studies indicated the presence of paranoia during both intoxication and withdrawal states. The cross-sectional studies revealed that the SC users were younger than the NC users, and the proportion of male users was higher among the SC users. Among the patients with psychosis, the SC-using population had significantly less severe negative symptoms. The studies assessing the association of depressive symptoms with SC use revealed mixed results, but there were significantly higher anxiety symptoms in SC users across the studies. One controlled administration study highlighted impaired motor performance and response inhibition in healthy volunteers after inhaling low-dose SC (2 milligrams of JWH-018). Despite the smaller sample size, methodological limitations, and lack of longitudinal studies, the deleterious impact of SC on mental health is quite obvious.[16] Panel 2 summarizes our current understanding about the synthetic cannabinoids and their psychiatric effects.

Cannabis withdrawal syndrome

Overview: Both the earlier reviews discussed the scepticism about whether cannabis can cause physiological dependence or a withdrawal syndrome significant enough to warrant a diagnosis.[5,6] They discussed how initial inconsistent evidence led to its exclusion from DSM-IV, and subsequent rigorous studies demonstrated clinically significant withdrawal symptoms, validating the existence of cannabis withdrawal syndrome (CWS). Ghosh and Basu's 2015 review also illustrated animal studies supporting biological plausibility, which led to the formal inclusion of CWS in DSM-5.[6] Bonnet and Preuss, 2017 have written an insightful narrative review outlining many CWS aspects.[17] In this review, we will try to add a few recent updates on CWS.

Panel 2: Synthetic cannabinoids and psychiatric disorders

Major issues:
- Synthetic cannabinoids like other designer drugs have frequently changing chemical structure.
- This makes them difficult to control legally as well as difficult to detect in biological samples.
- Cardiovascular, hematological, renal, and neuropsychiatric sequelae are common with SC exposure.
- Seizure can occur in up to 14–15% cases exposed to SC.

Psychiatric outcome:
- Compared to natural cannabis users, patients using SC have higher prevalence of psychosis, more severe positive symptoms.
- SC users experience more depressive and anxiety symptoms with respect to nonusers.
- Working memory, long-term memory, and cognitive inhibition are found to be significantly impaired in SC users in comparison to NC users.

Unresolved issues:
- What do the higher impairments mean? Do these reflect the altered pharmacological property of SC, or do they result from altered vulnerability of the users who expose themselves to SC?
- Is there any specific symptom profile associated with SC use? The comparison of severity of positive and negative symptoms in SC and NC group shows mixed result.
- Large-scale studies with robust methodology and sample size are still lacking to delineate the psychiatric effects of SC

Neurobiological Mechanisms: One review investigated neurobiological underpinnings of CWS involving the dysregulation of the endocannabinoid system, which plays a critical role in mood regulation, stress response, and reward processing. Chronic cannabis use leads to the downregulation of cannabinoid receptors, which exacerbates withdrawal symptoms upon cessation.[18] They also reported that females have been shown to have an increased rate and severity of a subset of cannabis withdrawal symptoms compared with men.

Symptom Trajectories and Predictors: Research has identified varying trajectories of CWS severity. Claus *et al*. (2023)[19] found two distinct patterns among cannabis-dependent individuals: One group exhibited a continuously decreasing severity of symptoms, while another experienced a sharp peak in symptoms between days 2 and 6 post cessation. Predictors of more severe withdrawal include younger age, a history of more intense cannabis use, and co-occurring substance use, particularly tobacco dependence.[20,21] Additionally, a study on young adults with psychiatric illnesses found that they may experience a delayed improvement in cannabis withdrawal symptoms compared to those without psychiatric diagnoses.[22] These factors contribute to the overall difficulty in managing withdrawal and achieving long-term cessation.

CWS in Medical Cannabis Users: Medical cannabis use has gained popularity in the recent past. While providing therapeutic benefits for conditions like chronic pain and anxiety, it carries the risk of developing CWS. Studies have consistently shown that medical cannabis users, similar to recreational users, can experience withdrawal symptoms upon cessation, including anxiety, irritability, sleep disturbances, decreased appetite, and cravings. These symptoms can be severe enough to disrupt daily functioning and increase the risk of relapse.[17,23]

The severity and manifestation of CWS vary widely depending on factors such as the frequency and duration of cannabis use, age, and the presence of co-occurring mental health conditions. Younger users and those with higher use frequencies are more likely to experience severe withdrawal symptoms.[20,24] This variability underscores the need for personalized management strategies when discontinuing medical cannabis to minimize withdrawal effects and support successful cessation. Healthcare providers should monitor for CWS in medical cannabis patients, offer support during

cessation, and consider alternative therapies to manage conditions without risking dependence and withdrawal.[25]

Treatment approaches

Pharmacological Interventions: Managing CWS often requires a combination of pharmacological and nonpharmacological strategies. Pharmacological approaches have included the use of guanfacine, which has been shown to reduce symptoms such as irritability and anxiety,[26] and gabapentin, which attenuates somatic signs like tremors and muscle stiffness.[27] Additionally, modulation of the endocannabinoid system using CB1-positive allosteric modulators has shown promise in reducing withdrawal symptoms without the psychoactive effects associated with direct CB1 agonists.[28] However, cannabinoid-based treatments, such as dronabinol, may reduce withdrawal symptoms but carry the risk of perpetuating dependence if not carefully managed.[25] An RCT demonstrated that nicotine patches might help reduce negative affective symptoms during cannabis withdrawal in individuals with CUD, regardless of their tobacco use status.[29] On the other hand, celecoxib, a COX-2 inhibitor, did not effectively reduce cannabis withdrawal symptoms or impact endocannabinoid levels in a clinical study.[30]

A systematic review evaluated pharmacological treatments for sleep disturbances associated with cannabis withdrawal. Seventeen studies (N = 562) were analyzed, revealing significant methodological limitations, small sample sizes, and high dropout rates. While Gabapentin, Lofexidine, Mirtazapine, Quetiapine, and Zolpidem showed some promise, the evidence is insufficient, and further research is needed to confirm their effectiveness.[31]

Nonpharmacological Interventions: Regular aerobic exercise has been found to improve sleep quality and reduce withdrawal-related disturbances.[32] Behavioral therapies, particularly cognitive-behavioral therapy (CBT), are also effective in helping individuals develop coping mechanisms to manage cravings and reduce the risk of relapse.

Challenges and Future Directions

Recent literature shows that the variability in withdrawal severity among individuals necessitates personalized treatment approaches. While pharmacological treatments can alleviate symptoms, their efficacy is often limited in terms of long-term relapse prevention. Future research should focus on developing more effective, targeted interventions that address both the physiological and psychological components of withdrawal, minimizing side effects and improving cessation outcomes. Panel 3 depicts the current conceptualization about cannabis withdrawal syndrome.

Panel 3: Cannabis Withdrawal Syndrome (CWS)

What was already known (pre-2015)?

- CWS was recognized as a clinical entity, having been included in the DSM-5.
- Prior research identified common symptoms such as irritability, sleep disturbances, decreased appetite, and cravings.
- Physiological basis of CWS was less understood compared to withdrawal syndromes from other substances, and there was limited research on the prevalence and severity of CWS across different populations.

What has been added/clarified during the past decade?

- There is robust evidence supporting the *validity of CWS as a distinct clinical syndrome*. Studies have clarified the *neurobiological mechanisms* underlying CWS, particularly the role of the endocannabinoid system in regulating withdrawal symptoms.
- Researches focus on *predictors of CWS severity*, such as frequency and duration of use, potency of cannabis, and individual factors like age and mental health status.
- CWS symptoms differs between recreational and *medical users, with medical users often experiencing milder symptoms*.
- New interventions have been *explored, with pharmacological treatments* like gabapentin and nonpharmacological strategies such as cognitive behavioral therapy (CBT) showing some promise in managing CWS, though no definitive treatment has emerged.

What remains unresolved

- Despite advances, there is still no consensus on the most effective pharmacological treatment for CWS, and long-term management strategies remain underexplored.
- The specific neurobiological pathways that differentiate CWS from withdrawal syndromes associated with other substances remain unclear.
- Further research is needed to assess the variability of CWS across different cannabis use patterns (e.g., high-THC vs CBD-dominant strains) and its prevalence in different populations, such as adolescents and those with co-occurring psychiatric conditions.

Cannabis and psychosis: The relationship

Cannabis as a component cause of psychosis: Earlier evidence indicates that cannabis serves as a component cause of schizophrenia, potentially triggering psychosis in vulnerable individuals. Recent studies further support these findings. A meta-analysis of 83 studies shows that cannabis use leads to symptoms 2.7 years earlier than in nonusers.[33] Another meta-analysis concluded that dose–response relationship exists, where the odds of developing psychotic symptoms were 3.9 times higher in heavy users compared to nonusers.[34]

Some evidence supports the reverse causality hypothesis, where cannabis use might be a consequence of psychosis. Cannabis may alleviate anxiety, negative symptoms, and mood, potentially making individuals with early signs of psychosis more likely to use it. A meta-analysis of 29 studies found that individuals at ultrahigh risk (UHR) for psychosis had significantly higher odds of lifetime cannabis use (OR 2.09) and current cannabis use disorder (OR 5.49). The study also noted more severe positive symptoms (suspiciousness, unusual thoughts) in cannabis-using UHR individuals than nonusers, suggesting a vicious cycle of increased cannabis use and heightened psychotic symptoms.[35] Another recent meta-analysis of 55 studies conducted across Europe, America, and the Western Pacific region examined the link between substance use and psychotic-like experiences (PLE) in youth (≤17 years). Results showed that youth with PLE

were twice as likely to use substances, with a 1.99 times higher odds of lifetime cannabis use and 2.25 times higher odds of weekly cannabis use compared to those without psychotic symptoms. This emphasizes an elevated risk of cannabis use in adolescents with psychosis risk, especially with frequent use.[36]

Cannabis and the course of psychosis: Early cannabis exposure has been linked to a worse course of psychotic illness. A meta-analysis of 24 studies conducted across 3 decades concluded that continued cannabis use predicted poorer outcomes, a higher relapse rate, longer hospitalization, and more severe positive symptoms in patients with psychotic disorders.[37] A third-decade follow-up of the well-known Swedish conscript study found that schizophrenia patients with a history of cannabis use had longer hospital stays and more frequent hospitalizations, though their symptom profiles were similar to those of nonusers.[38,39]

A study on 678 Dutch patients showed that persistent cannabis use was associated with higher positive and general symptoms (on the PANSS scale) and poorer functionality over the 3-year follow-up period in patients with nonaffective psychosis.[39,40] In a UK-based study on 127 FEP, cannabis use was associated with poorer PANSS total, PANSS negative score, depression score, and psychosocial functioning even adjusting for potential sociodemographic, clinical, and substance-related confounders.[41]

This nature of guarded prognostic effect is not consistent across studies. A study explored the effects of cannabis and alcohol on the longitudinal course of first-episode psychosis (N = 192) and symptoms profile: CUD or problematic use was not associated with higher PANSS or CDSS scores. Ceasing cannabis use was associated with a lower PANSS score in baseline and at 12 months, but this effect weaned at 24 months.[42] Studies also indicate that CUD comorbidity increases treatment nonadherence.[43] However, a UK study noted similar treatment response rates in psychotic patients with and without cannabis use, though relapse rates were higher with heavier cannabis use.[44] Figure 3 summarizes the effect of cannabis on the onset and course of psychotic spectrum disorders.

The diagnostic stability of cannabis-induced psychosis: CIP is often a provisional diagnosis, with clinicians needing to reassess after cannabis abstinence. If psychosis persists, the diagnosis should be revised to independent psychosis with comorbid CUD. At least two studies shed light on diagnostic stability of CIP. A Danish registry study showed that around one-third of patients with substance-induced psychosis transitioned to independent psychosis, with the rate being 50% for those with CIP.[45] Another study in India found that while cannabis-induced mood disorder remained stable, half of the CIP cases converted to independent psychosis (41%) or affective disorders (9%).[46]

Cannabis potency and psychosis

Presently, the discussions of the relationship of cannabis and schizophrenia mostly revolve around that of THC and schizophrenia as THC is the main psychoactive cannabinoid. In contrast, the other constituent CBD has antipsychotic properties. Studies across the globe have proven that acute

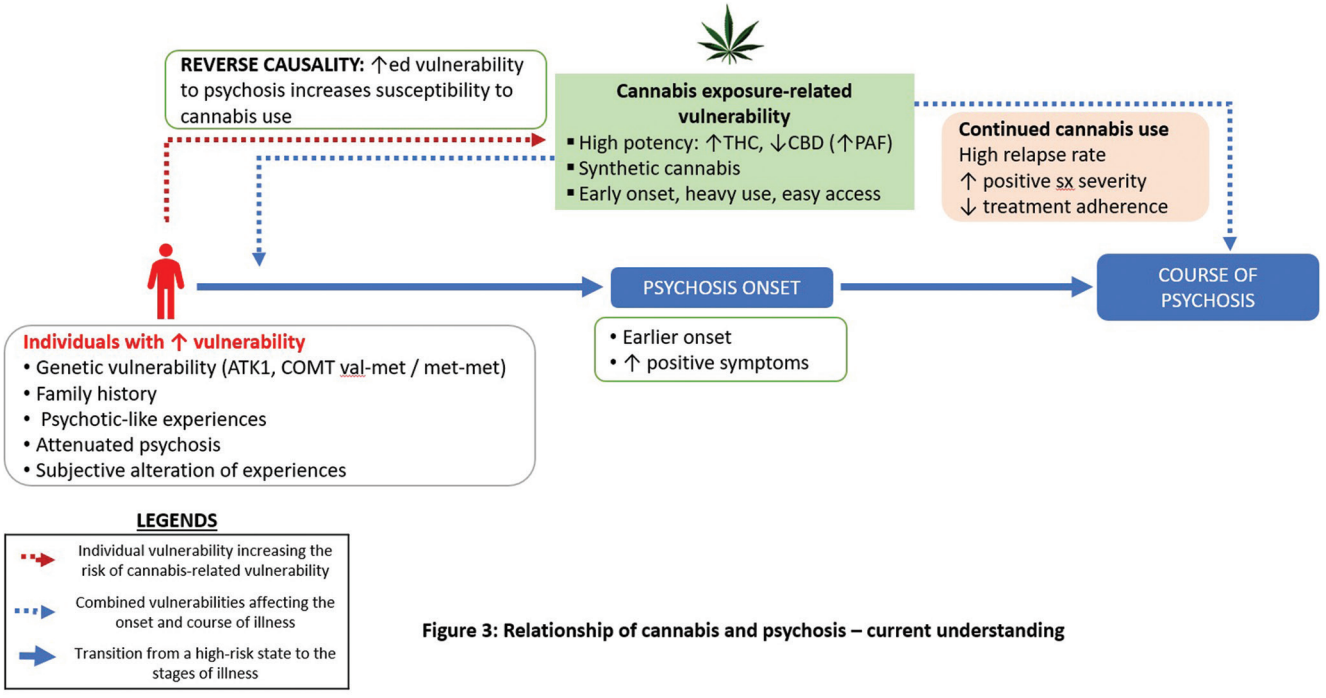

Figure 3: Relationship of cannabis and psychosis – current understanding

Figure 3: Relationship of cannabis and psychosis - current understanding

administration of THC in nonpsychotic subjects can induce a wide array of psychotic symptoms. A meta-analysis of 15 studies published between 2004 and 2018 showed that a single administration of THC in a healthy subject can induce a wide array of positive, negative, and general symptoms of psychosis. CBD had no consistent relationship with psychotic symptoms.[47]

How much cannabis is too much? Dose–response relation between cannabis use and psychotic symptoms is often confusing as there are many potential confounding variables. Vulnerability to psychotic illness, potency of cannabis used, and THC: CBD ratio in the cannabis preparation can affect the dose–response relationship. Despite that, multiple studies tried to explore the same, and a comprehensive review and meta-analysis in 2016 attempted to answer this question conclusively. Ten studies, conducted across Europe, North America, and Australia, were included in the meta-analysis. There was a consistent increase in the risk of psychotic symptoms associated with higher cannabis exposure (in terms of increased frequency and higher dosage). The odds ratio for the development of psychosis in some cannabis use with respect to no cannabis use was 1.97 (CI 1.68–2.31), whereas the same increases to 3.9 (CI 2.84–5.34) in the most severe cannabis use. The result is similar in both the cohort and cross-sectional studies and across different measures of psychosis outcome.[34]

High-potency cannabis is becoming more common across Europe and North America. The potency of cannabis depends on the δ9 THC concentration. Since 2000, the potency of cannabis increased by around four times in various parts of the world. Currently, the higher potency cannabis contains >10% THC, whereas Skunk variants contain around 13% THC and a popular variant in Colorado, named Girl Scout Cookies, contains 28% THC. A more disturbing fact is that cannabidiol (CBD) concentration is reduced in plants that produce more THC.[48]

How does high-potency cannabis affect the population in terms of psychotic symptoms? The impact of high-potency cannabis use can be assessed indirectly with a comparison of cannabis exposure between persons with first-episode psychosis and without psychosis. This kind of comparison can generate population attributable fraction (PAF). This denotes the portion of psychosis, which can be prevented by the exclusion of high-potency cannabis. A part of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study has assessed PAF of high-potency cannabis in a multicenter study across the European Union (EU) and Brazil. Overall, daily cannabis use was associated with 3.2 times higher odds of psychosis in comparison to never-users. Overall, the PAF was 12.2%, suggesting that 12.2% of first-episode psychosis could have been prevented if high-potency cannabis was not available. This estimation shot up to around 30% in London and 50% in Amsterdam sites, suggesting immense public health implications of reduction of high-potency cannabis exposure.[49] Panel 4 summarizes the existing knowledge, recent advances, and current controversies regarding the relationship between cannabis and psychosis.

Cannabis and mood disorders

Mood dysregulation is common with CUD. Often young adults use cannabis as self-medication for their pre-existing depressive and anxiety symptoms. These users often resort to heavy cannabis. Interestingly, some recent studies suggested that self-medication is more common in the states with medical cannabis laws, whereas the finding is not consistent across studies.[50,51] A large number of cannabis users reported of having at least a short-term improvement in depressive symptoms after cannabis use.[52] Cannabis withdrawal also overlaps with depressive symptoms, leading to cannabis self-administration. Despite the understandable links between cannabis and mood disorders, there is a lack of well-controlled longitudinal studies to establish the same.

Panel 4: Cannabis and Psychosis

What was already known (pre-2015)?

- Cannabis use is associated with an increased risk of developing psychosis, particularly in vulnerable individuals.
- Early and heavy cannabis use could precipitate psychotic episodes and possibly accelerate the onset of schizophrenia.
- Cannabis use during the course of psychosis is associated with poor outcome, high relapse rate, more severe positive symptoms, and poor treatment adherence
- The relationship between high-potency cannabis and psychosis was emerging but not well defined.
- A section of cannabis-induced psychosis converts to independent psychosis in their longitudinal course

What has been added/clarified during the past decade?

- Newer studies have provided more substantial evidence linking cannabis use, especially high-potency strains, to an increased risk of psychosis. Population-attributable risk (PAR) for cannabis-induced psychosis is now better quantified, especially postlegalization in regions like Canada.
- Reverse causality hypothesis suggests that those vulnerable to develop psychosis are more prone for regular cannabis use.
- Those who are at ultrahigh risk for psychosis and those with psychotic like experience are more likely to use cannabis compared to their normal counterpart.
- Advances in genetic studies have illuminated gene–environment interactions, showing that individuals with certain genetic profiles (e.g., AKT1 and COMT gene variants) may be more susceptible to cannabis-induced psychosis.

What remains unresolved

- The specific mechanisms by which cannabis triggers psychosis in genetically vulnerable individuals remain unclear.
- It is still uncertain whether psychosis risk differs significantly across different patterns of cannabis use (e.g., medical vs recreational OR occasional vs regular) and in regions where cannabis has been legalized.

Cannabis and bipolar disorder (BD)

Cannabis use is known to be associated with BD. The prevalence of BD in patients with cannabis use disorder was found to range between 3.3% in the Scandinavian countries and up to 14.6% (BD I) and 2.7% (BD II) in US.[53,54] Around a third of the patients with BD use cannabis, whereas a meta-analysis revealed around 20% of patients with BD have cannabis use disorder.[55] One systematic review in 2014 synthesized 53 studies conducted between 1972 and 2013. The review suggested that around 70% of patients with bipolar disorder used cannabis in their lifetime, and around a third of them had cannabis use disorder. Cannabis use was associated with earlier onset of the first manic episode, more frequent mood episodes, higher risk of rapid cycling, and overall poorer prognosis of BAD.[56]

Current knowledge base and lacunae about the relationship between cannabis and bipolar affective disorders: Till the past decade, the handful of studies to establish the relationship between cannabis use and bipolar disorders showed predominantly significant associations. The study findings suggested that early and heavy cannabis use is associated with bipolar affective disorder episodes, even after adjustment of potential confounding factors. Early cannabis use appears to bring forward the onset of bipolar disorder.[57] Besides, continued cannabis use appeared to affect the course of bipolar disorders adversely. The limited evidence suggested no reverse causality. One large-scale longitudinal Swedish study reported no association between cannabis use and bipolar disorder, and their study findings suggest that the association between cannabis and subsequent mood symptoms is due to common risk factors like premorbid temperament and other substance use.[58]

Cannabis use and the onset of bipolar disorder: At least four large-scale studies in the past decade explored the relationship between cannabis and bipolar disorders.[59,60] The Finnish birth cohort study also found a significant association between cannabis use during adolescence and subsequent diagnosis of bipolar disorder. The significance is retained when controlled for the gender, family history, and self-report of the extent of cannabis exposure, but when the use of alcohol and other substances is considered, the significance is lost. As a result, the authors concluded that the relationship of cannabis and bipolar disorder is confounded by other substance use.[61] The secondary analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) data also revealed no significant association between cannabis use and bipolar disorders.[62]

Cannabis use and the course of bipolar disorder: Relatively fewer studies have assessed the effect of cannabis on the course of bipolar disorder. The last decade's studies also underline the adverse impact of cannabis on the course of BD, in terms of more severe psychopathology, poorer treatment adherence, higher suicidality, and rapid cycling BD.[63]

Cannabis and depressive disorders

Earlier studies assessing the relationship between cannabis and depressive disorders showed that cannabis use was significantly common in patients with depressive disorders and vice versa.[64] Besides this, studies reported a significant association of major depressive disorders with early and heavy cannabis use to no substantial association between depressive disorders and cannabis use.[58,65]

Cannabis and depression: the association: Recent studies exploring the relationship between cannabis use and depression revealed mixed results. The literature on cannabis and psychopathology exhibits random multiformity, referring to the heterogeneous and often unpredictable nature of associations observed across studies. This variability arises due to differences in study designs, sample characteristics, assessment methods, and definitions of cannabis use and psychiatric outcomes. Such inconsistencies contribute to the difficulty in drawing definitive causal conclusions as findings may vary depending on methodological and population-related factors. A recent genetically informed study aiming to model the nature of this association revealed that CUD could be causally associated with major depressive disorder (MDD), or there might be a random multiformity for both disorders. The random multiformity indicates that being above the threshold for one disorder (CUD or MDD) increases the threshold of the other disorder.[66] Various large-scale studies highlighted that early and frequent cannabis use was associated with major depressive disorders and suicidality.[67–69] This association was not entirely explained by the confounders like shared genetic vulnerability and early family environment in the concordant and discordant twins.[70] A study on Canadian teenagers revealed that the association between cannabis and depressive disorders is bidirectional as early cannabis use predicted depressive symptoms later, and vice versa. Sexual minorities had a significantly stronger association between early depressive symptoms and later cannabis use, which may indicate self-medication.[71] Another US-based study explored the relationship of dysthymia with cannabis use and CUD across the decadal birth cohorts from 1940 to 1990. Dysthymia had a significant association with both cannabis use and CUD. The association between cannabis use and dysthymia gradually weakened across the past 6 decades of birth cohorts, whereas the same between CUD and dysthymia remained unchanged.[72] These pieces of evidence suggest a significant association of early and heavy cannabis use with depressive disorders, with a possibility of a bidirectional relationship between the two entities.

There are multiple studies that either highlighted a reverse association or failed to find an association between cannabis use and depressive disorders. A longitudinal Swedish birth cohort study of 8598 persons (age range 20–64 years) revealed no direct or reverse causal association between cannabis use and depressive or

anxiety symptoms, after adjusting for alcohol and other substance use.[73] The secondary analysis of NESARC data also reveals similar results, and the studies showed that except for alcohol and stimulants, the other SUDs (i.e., tobacco, cannabis, opioids) had similar incidence rates of depressive and anxiety disorders.[62,74] A study on Canadian teenagers revealed that the association between cannabis use and later suicidal thoughts can be fully explained by other substance use. Depression was found to predict cannabis use in subsequent years.[75] All these studies assessed cannabis use in young adults or later. So, current evidence suggests a minimal association of later cannabis use, with MDD, or MDE causing cannabis use in older populations.

How does cannabis affect the course of depression? As discussed earlier, the causal relationship of early and heavy cannabis use for developing subsequent MDD suggests that cannabis abstinence should attenuate MDD symptoms. A recent systematic review suggested that 4 weeks of abstinence from cannabis improved MDD symptoms in a Canadian population. Reversibly, continued use of medical cannabis was observed to worsen the depressive symptoms. These imply that cannabis adversely affects the course of the MDD. One important limitation of the research in this regard is the absence of a comparison group with continued cannabis use.[63] Figure 4 summarizes the effect of cannabis on the onset and course of affective disorders.

What underlies the association between cannabis use and mood disorders? The Genome-wide association studies (GWAS) and Mendelian randomization studies support the common vulnerability hypothesis underlying cannabis and mood disorders. There is an overlap of genetic liability between CUD and MDD, and the shared vulnerability between CUD and MDD also plays a major role in the association between these entities.[76] An Australian twin registry study attempted to elicit the direction of causality between CUD and MDD. It appeared that either CUD causes MDD, or the risk factors of CUD after a certain threshold can increase the risk of MDD (multiformity of risk factors).[66] Studies suggested the shared genetic vulnerabilities underlying cannabis use, CUD, depression, MDD, and self-harm,[77–79] but the extent of association is rather small, which suggests a significant role of environmental factors and gene–environment interaction in developing the CUD and depression comorbidity. Panel 5 summarizes the existing knowledge, recent advances, and current controversies regarding the relationship between cannabis and mood disorders.

Cannabis use and suicidality

Overview: Some recent studies, including systematic reviews and meta-analyses, suggest that cannabis use may elevate the risk of suicidal behaviors, particularly in adolescents and individuals with CUD.

Cannabis use, Suicidal Ideation, and Attempts: Research indicates a strong link between cannabis use and an increased risk of suicidal ideation and attempts.[80,81] In a

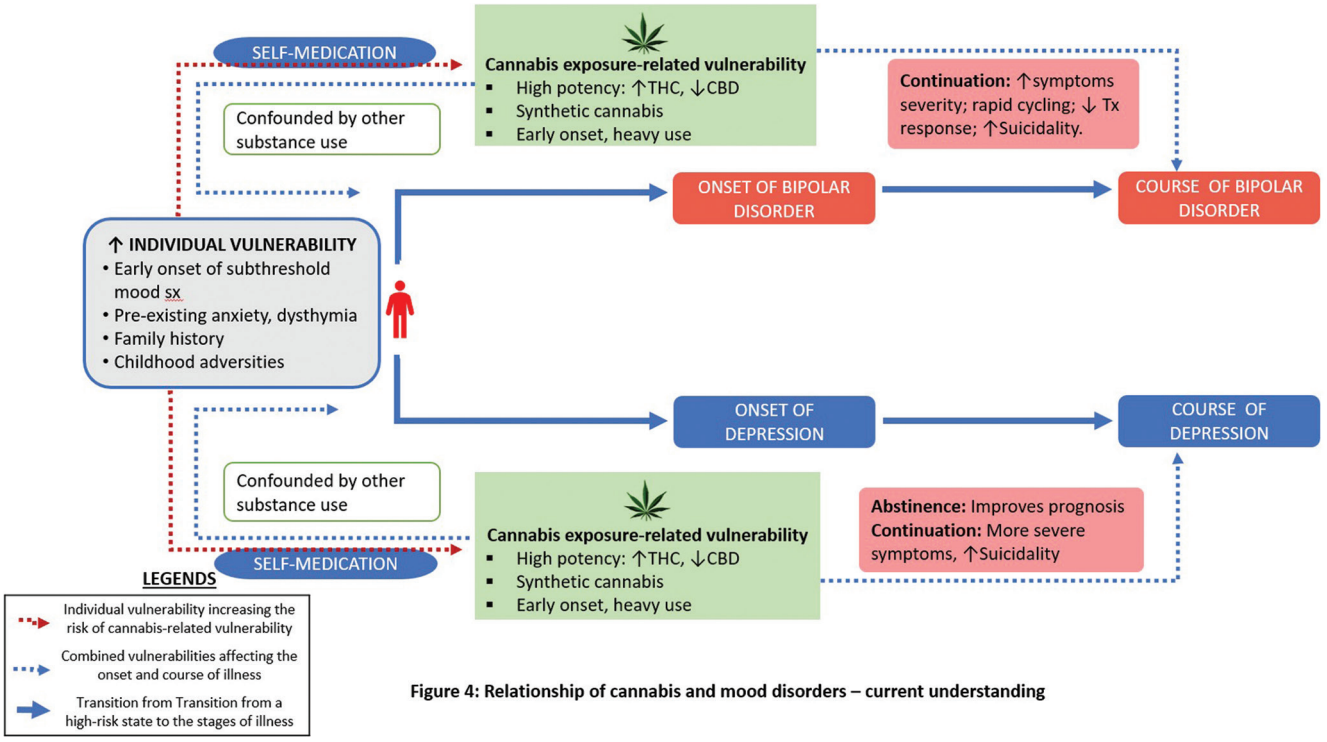

Figure 4: Relationship of cannabis and mood disorders – current understanding

Figure 4: Relationship of cannabis and mood disorders - current understanding

Panel 5: Cannabis and Mood Disorders

What was already known (pre-2015)?

- Cannabis use was linked to mood disorders, particularly depression and bipolar disorder (BD).
- Patients with pre-existing anxiety and depressive disorders are prone to use cannabis for self-medication.
- Direction of causality (whether cannabis use led to mood disorders or vice versa) was not fully established, and evidence was mixed.

What has been added/clarified during the past decade?

- Longitudinal studies have provided stronger evidence of a bidirectional relationship between cannabis use and mood disorders, particularly BD.
- Early onset and heavy cannabis use increase the vulnerability to develop affective disorders.
- Continued use has been shown to worsen the course of mood disorders, especially in individuals predisposed to depression or BD.
- New findings suggest that genetic vulnerabilities (e.g., specific gene variants) may predispose some individuals to both CUD and mood disorders.

What remains unresolved

- The exact biological mechanisms that link cannabis use with mood disorders are still poorly understood.
- Further research is needed to assess how cannabis interacts with treatments for mood disorders, such as antidepressants and mood stabilizers, and whether certain populations are more vulnerable to the negative effects of cannabis on mood.

meta-analysis, Fresán *et al*. (2022)[82] found that cannabis use significantly raises the risk of suicidal ideation (OR: 2.04; 95% CI: 1.64-2.53) and attempts (OR: 2.33; 95% CI: 1.78-3.05) among adolescents. Additionally, Jacobs *et al*. (2023)[83] highlighted that in adolescents, the concurrent use of cannabis and other substances further exacerbates the risk of suicidal behaviors.

Cannabis Use Disorder and Suicidality: CUD is strongly linked to an increased risk of suicidality. Research by Adkisson *et al*. (2019) and Grove *et al*. (2023) indicates that veterans with CUD, including those from the Iraq/Afghanistan and Gulf War eras, are significantly more likely to attempt suicide, with adjusted odds ratios (AOR) of 7.963 and 2.15, respectively, compared to their counterparts without CUD.[84,85] This heightened risk is not limited to veterans; Oladunjoye *et al*. (2023)[86] found that individuals with CUD in the broader U.S. population also face an increased risk of suicide attempts (OR = 1.4, 95% CI 1.3-1.6, $P < 0.001$).

Cannabis-Induced Psychosis and Suicide Risk: Cannabis-induced psychosis significantly elevates the risk of subsequent suicide attempts. In the Danish prospective register-based cohort study, Munch *et al*. (2023)[87] reported a hazard ratio of 8.9 for suicide attempts in individuals with cannabis-induced psychosis, highlighting the need for targeted interventions in this vulnerable group.

Demographic and Psychosocial Factors: Demographic factors such as age and sex influence the relationship between cannabis use and suicidality. Female adolescents who use cannabis are at a particularly high risk, as shown by Jacobs *et al*. (2023) and Hodgson *et al*. (2020).[83,88] The psychosocial context, including the intensity of cannabis use, also plays a crucial role in suicide risk.[89,90]

Clinical Implications: The strong association between cannabis use, particularly CUD, and suicidality—even in the absence of overt mood symptoms—highlights the critical need for routine screening and early intervention in at-risk populations. Further research should focus on the mechanisms underlying this link, including genetic and environmental factors, to inform more effective prevention strategies.

Effect of prenatal cannabis exposure (PCE)

With increasing legalization and normalization of cannabis use in different parts of the world, concerns have grown regarding its safety during pregnancy. This section synthesizes key findings related to PCE's impact on pregnancy outcomes, fetal growth, neurodevelopment, and cognitive and behavioral outcomes.

Adverse pregnancy and growth-related outcomes

Several studies demonstrate an association between PCE and negative pregnancy outcomes. A recent meta-analysis reported a higher risk of preterm birth (PTB; adjusted OR 1.42), small for gestational age (SGA; aOR 1.76), and perinatal mortality (aOR 1.5).[91] Another meta-analysis of 57 studies also found increased NICU admissions, particularly for infants with coexposure to tobacco.[92] Additionally, A cumulative meta-analysis by Tadesse *et al*. (2024)[93] identified structural birth defects linked to PCE, with odds ratios (OR) of 2.35 for cardiovascular defects and 2.87 for central nervous system defects. A retrospective population-based cohort study reported that coexposure to cannabis and nicotine exacerbated these risks, elevating rates of infant death and PTB [Adjusted Rusk ratio (aRR) =2.18 for infant death, aRR = 1.83 for preterm delivery].[94] However, Dana Watts *et al*. (2024)[95] found no significant association with birth weight or gestational age after adjusting for confounders, indicating that some earlier studies may have overstated the adjusted risk ratio.

Neurodevelopmental effects of PCE and autism

PCE is also linked to neurodevelopmental challenges, specifically autism spectrum disorder (ASD). A meta-analysis included four studies on ASD encompassing 222,534 mother–offspring pairs. It found an increased risk of ASD, with significant associations between PCE and ASD (RR = 1.30).[96] Notably, male offspring showed a stronger association with ASD risk, suggesting sex-based differences in susceptibility. Avalos *et al*. (2024)[97] also explored PCE's association with autism, though their results were inconclusive (hazard ratio [HR], 1.05; 95% CI, 0.84-1.32).

Neuroimaging studies show PCE-related changes in brain structures, particularly in white matter pathways involved

in emotion and memory, suggesting potential long-term impacts on neurodevelopment.[98] While some studies yield mixed findings, Nutor *et al*. (2023)[102] conducted a large-scale investigation across multiple cohorts. They found no consistent increase in ASD traits linked to PCE after controlling for other factors, such as prenatal tobacco exposure. These variations in findings underscore the importance of adjusting for coexposures and demographic factors to obtain a more accurate picture of PCE's effects on autism risk.

Cognitive and behavioral outcomes

The effects of PCE on cognitive and behavioral outcomes remain debated. Tadesse *et al*. (2024)[96] conducted a meta-analysis, finding that prenatal cannabis exposure (PCE) increased the risk of ADHD by 1.3 times ($\beta = 0.39$). Baranger *et al*. (2024)[99] found that PCE is associated with changes in brain regions linked to ADHD and attention problems. The same group also analyzed data from the ABCD Study, examining over 10,000 adolescents to assess the effects of prenatal cannabis exposure (PCE) on mental health. They reported that PCE increased the risk of externalizing behaviors, including rule-breaking and impulsivity, with specific metrics indicating that PCE-linked brain changes accounted for approximately 1.5–2% of these psychopathology outcomes. These findings highlight the subtle yet significant long-term mental health risks associated with cannabis exposure during pregnancy.[100] Dana Watts *et al*. (2024)[95] identified a potential association between PCE and communication delays at 12 months, though this weakened after adjusting for multiple comparisons.

A meta-analysis by Sorkhou *et al*. (2024)[92] found no significant cognitive impairments beyond increased externalizing behaviors and attention deficits, while Trammel *et al*. (2024)[101] reported that PCE alone did not predict adverse neonatal outcomes. However, infants exposed to both cannabis and tobacco showed attention problems.

Considerations and public health implications

With rising cannabis use during pregnancy, public health interventions must address the risks of PCE. Nutor *et al*. (2024)[102] highlight the importance of considering coexposures, especially tobacco, in assessing cannabis-related risks. Enhanced preconception counseling is essential to mitigate risks of birth defects and growth-related outcomes linked to PCE. Despite some conflicting findings, the cumulative evidence supports advising against cannabis use in pregnancy due to potential long-term risks.

Scope for future studies

Several gaps in the literature need to be addressed:

1. *Longitudinal Studies*: Extended follow-up into adolescence and adulthood is necessary to fully understand the lasting effects of PCE on cognitive and behavioral development.
2. *Dose–Response Relationships*: More research is needed to clarify how different levels of cannabis exposure, from occasional to heavy use, affect developmental outcomes.
3. *Co-Exposure to Other Substances*: Studies controlling for substances like tobacco and alcohol will help isolate the specific impact of cannabis exposure.
4. *Epigenetic and Molecular Mechanisms*: Noble *et al*. (2024)[103] highlighted the need to explore epigenetic changes associated with PCE, which may offer insights into how cannabis affects neurodevelopment at the molecular level.

Future studies addressing these areas will improve guidance for clinicians and public health professionals, helping to protect maternal and child health.

Cannabis policy and its effect on cannabis-related psychopathology

Cannabis policy changes, particularly reforms such as legalization, have been implemented in various regions to reduce the legal and social burdens associated with cannabis use. A study from Uruguay, the first country to legalize recreational cannabis, focuses on policy impact on adolescent use rather than cannabis-related psychopathology.[104] They found no short-term increase in cannabis use but highlighted increased perceived availability. Canada, the first G-20 country to legalize cannabis in 2018, reported an increase in prevalence from 22% in 2017 to 27% in 2022.[105] This section examines the effects of legalization on cannabis-related psychopathology, including psychosis, suicidal behavior, emergency visits, and road traffic accidents (RTAs), using data from both Canada and the United States.

Cannabis-related psychosis and mood disorders

Cannabis-induced psychosis has been a major concern in regions that have legalized cannabis. Studies from both the U.S. and Canada report an increase in cannabis-related psychiatric conditions post legalization. In Canada, the legalization led to a 30% increase in cannabis-induced psychosis cases in Ontario emergency departments.[106] Similarly, a time-series analysis found that cannabis-induced psychosis doubled in Alberta and Ontario following legalization.[107]

In the U.S., Zvonarev *et al*. (2019)[108] reported an increase in hospitalization for psychiatric disorders, particularly among young cannabis users in legalized states. Fischer *et al*. (2022)[109] emphasized that reductions in crime related to cannabis possession may be offset by the increased burden on mental health services in Canada. However, Zellers *et al*. (2023)[110] found no significant increase in psychiatric disorders, including psychosis, in Oregon following legalization. This variation highlights the importance of considering local policy, accessibility, and population factors.

Cannabis-related suicidal attempts

Cannabis use has been linked to suicidal ideation and attempts, though findings are mixed in regions with legalized cannabis. A longitudinal study in Alberta found no significant increase in cannabis-related suicidal attempts post legalization.[106] Similarly, Scheim *et al*. (2020)[111] reported no clear correlation between cannabis legalization and increased suicidal attempts in U.S. states such as Washington, where cannabis was legalized in 2012.

Emergency room visits

In Canada and the U.S., emergency room visits for cannabis-related issues have risen substantially since legalization. In Ontario, the commercialization of cannabis products, including edibles and concentrates, led to a 22% rise in cannabis-related emergency department visits by 2021.[106,107] Studies from USA and Canada reported a significant increase in cannabis hyperemesis syndrome cases.[112,113] Likewise, Colorado saw a 300% increase in cannabis-attributable emergency department visits, with patients often presenting with acute intoxication, anxiety, and psychosis.[114]

Road traffic accidents

One of the most concerning public health consequences linked to cannabis legalization is the increase in RTAs. Colorado also experienced a 100% increase in traffic fatalities involving cannabis-impaired drivers post legalization.[114]

According to the Canadian Cannabis Survey, between 2017 and 2021, the percentage of cannabis users driving within 2 hours of smoking decreased from 29% to 22%, peaking at 32% in 2019.[106] A time-series analysis in Alberta and Ontario showed no significant impact of cannabis legalization on emergency visits for traffic-related injuries, even among youth drivers. While overall rates of cannabis-impaired driving stabilized or declined slightly,[105] Brubacher *et al*. (2022)[115] documented a 2.29-fold increase in THC detection among drivers involved in traffic injuries in British Columbia after legalization. These findings underscore the need for more robust public awareness campaigns and more effective enforcement of impaired driving laws.

The increase in emergency room visits and cannabis-related road traffic accidents, particularly after the commercialization of high-potency edibles and concentrates, points to a public health concern that extends beyond psychiatric conditions. Fischer *et al*. (2022)[109] argue that more comprehensive data are needed to assess whether this rise is directly attributable to legalization or part of broader societal trends.

Cannabis and Opioid Use Disorder or Problematic Use

There is ongoing debate about whether cannabis legalization might mitigate opioid use disorder or problematic use. Wendelboe *et al*. (2019)[116] observed a 6.5% reduction in opioid overdose deaths in U.S. states like Colorado post legalization. However, in Canada, there is little evidence to suggest that cannabis legalization has had a significant effect on opioid use rates, raising questions about the potential for cannabis as a substitute for opioids.[106]

Meanwhile, in Canada, concerns about a potential rise in adolescent cannabis use post legalization have not been realized. However, youth cannabis consumption has remained stable, contrasting with the decreasing trends seen in alcohol and tobacco use.[117]

Summary

While the legalization of cannabis has not resulted in a formally declared public health crisis, it has led to notable public health concerns. A threefold increase in emergency department visits for cannabis-related issues meets the epidemiological threshold for a significant rise in health service utilization. Moreover, the intended public health goals of legalization—such as reducing problematic cannabis use and its associated harms—have not been fully realized. The social justice outcomes—such as reducing cannabis-related criminal penalties/arrests—appear more favorable than the public health outcomes.[118,119] Taken together, these mixed findings highlight the need for more nuanced future research on cannabis-related psychopathology. Panel 6 depicts the current conceptualization about impact of the change in cannabis policy on public mental health.

Cannabis and cognitive function

Overview of Cognitive Impairments: Ghosh and Basu's previous review (2015) discussed the impact of cannabis use on

Panel 6: Policy Implications and Public Health

What was already known (pre-2015)?

- Public health concerns were focused on the social and legal consequences of cannabis use, particularly in regions where it remained illegal.
- Limited data existed on the impacts of legalization on public health outcomes as only a few regions (e.g., certain U.S. states) had moved toward decriminalization or legalization.

What has been added/clarified during the past decade?

- The past decade has seen the legalization of cannabis in several regions, providing new data on public health outcomes. Research from Canada, the U.S., and Uruguay has shown mixed results.
  - There is a reduction in cannabis-related crime.
  - The increase in cannabis use in young population indicated possibility of exacerbation of cannabis-related harms.
  - There is increased prevalence of cannabis-induced psychosis, emergency room visits, and road traffic accidents in some areas.
- The rise of high-potency cannabis products has been linked to increased public health risks, particularly among youth and heavy users.

What remains unresolved

- The long-term public health effects of widespread cannabis legalization remain unclear, particularly with regard to high-potency products and their impact on vulnerable populations (e.g., adolescents, those with mental health disorders).
- More research is needed to assess the effectiveness of harm-reduction policies and education campaigns in mitigating the negative consequences of legalization.

cognitive functions in detail.[6] Here, we will highlight key updates in this area over the past decade.

Increased understanding of specific cognitive deficits

Memory impairment in acute intoxication: Memory impairment is one of the most pronounced cognitive effects of cannabis use. Studies indicate that both acute and chronic cannabis use impair various aspects of memory, including encoding, consolidation, and retrieval processes. Ranganathan *et al*. (2017),[120] in a double-blind RCT, demonstrated that THC impairs memory encoding but not retrieval, highlighting the specificity of its effects on cognitive processes. The meta-analysis by Schoeler *et al*. (2016)[121] found that cannabis use significantly impairs memory function, particularly in healthy individuals' global memory, prospective memory, and verbal and visual recall. In contrast, individuals with psychosis showed some memory improvements with cannabis use, such as in visual recall. The severity of memory impairments in healthy users was influenced by age, duration of use, and abstinence, with younger users and those abstinent for longer experiencing less impairment.

Memory impairment in chronic intoxication: McClure *et al*., 2015[122] reported that chronic cannabis users often exhibit significant deficits in verbal learning and memory, as demonstrated by poorer performance on standardized memory tests. Interestingly, those who reported minor memory problems performed better on objective memory tasks than those reporting no or serious issues, suggesting a disconnect between self-perceived and actual memory impairments, with some adolescents potentially underestimating their cognitive deficits. On the other hand, a study on first-episode psychosis by De Vos *et al*. (2020)[123] found no significant differences in cognitive performance, including verbal memory, verbal fluency, and attention, between cannabis users (CU) and nonusers.

Executive Function and Attention: A scoping review by Ayoub *et al*. (2024)[124] in people with HIV highlighted the mixed evidence on the impact of cannabis on executive functions in these people. Adverse effects on EF were mainly linked to heavier cannabis use or specific EF subdomains, such as risky decision-making. Bhattacharyya *et al*. (2015)[125] provided experimental evidence that impairments in cognitive processes were related to the inhibitory control of thoughts and actions, along with inferior frontal functions under the influence of cannabis.

Blest-Hopley *et al*. (2019)[126] conducted a meta-analysis to examine the effects of regular cannabis use on brain function, mainly focusing on adolescent users. The study found that even after a prolonged period of abstinence (over 25 days), adolescent cannabis users exhibited altered activation in key brain regions associated with the central executive and default mode networks compared to nonusers.

More Insight on neurobiological mechanisms

Recent studies shed light on neurobiological mechanisms underlying these cognitive impairments. A double-blind RCT by Colizzi *et al*. (2018)[127] found that individuals with modest prior cannabis use exhibited reduced psychotomimetic effects and cognitive impairments as well as less disruption in brain activity when exposed to Δ9-THC compared to nonusers. This suggests that even modest cannabis use can lead to tolerance, diminishing both behavioral and neurophysiological responses to Δ9-THC.

Functional MRI studies, such as those by Dager *et al*. (2018),[128] have shown altered activation patterns in brain regions associated with memory and executive functions in cannabis users. These alterations include decreased activity in the prefrontal cortex and hippocampus, areas crucial for cognitive control and memory formation.

Effects of abstinence and recovery

A systematic review by Ganzer *et al*. (2016)[129] found that chronic cannabis use leads to significant and persistent impairments in memory, attention, and executive functions, particularly in heavy and long-term users, even after periods of abstinence. However, there is recent evidence suggesting that some cognitive deficits associated with cannabis use may improve with sustained abstinence. Sorkhou *et al*. (2022)[130] found that a 28-day period of cannabis abstinence led to improvements in visual search speed, selective attention, and visuospatial working memory in individuals with major depressive disorder and comorbid cannabis use disorder. Similarly, Venero Hidalgo *et al*. (2022)[131] noted that while memory functions improved with abstinence, attention deficits persisted, indicating a differential recovery trajectory for various cognitive domains.

Psychosis and cognitive outcomes

The impact of cannabis on cognition can vary depending on individual factors such as age of onset, frequency of use, and genetic predisposition. The meta-analysis by Bogaty *et al*. (2018)[132] has shown that young adults with early onset cannabis use and psychosis exhibit poorer cognitive performance compared to nonusers with psychosis, particularly in domains such as verbal learning, working memory, and motor inhibition. The cognitive deficits in were more pronounced with increasing age.

Additionally, a systematic review by Gicas *et al*. (2022)[133] suggests that cannabis-induced psychosis (CIP) may involve distinct cognitive impairments similar in magnitude to those observed in schizophrenia. This highlights the need for more rigorously controlled studies to understand better the cognitive phenotype associated with CIP.

To summarize

The newer literature offers more detailed insights into the specific cognitive deficits caused by cannabis, explores

the neurobiological underpinnings with greater precision, and considers the potential for cognitive recovery with abstinence. Additionally, the role of age of onset and genetic factors has been investigated, offering a more comprehensive view of how cannabis impacts cognitive functions across different populations. These additions help to create a more nuanced and clinically relevant understanding of the cognitive effects of cannabis, which is critical for informing both research and treatment approaches. Panel 7 enumerates the current advances in the conceptualization of cognitive effects of cannabis, with the lacunae of our knowledge.

Cannabis, psychopathology, and genetics

Recent research highlights the complex interplay between cannabis use, genetic predispositions, and psychopathology. Genetic polymorphisms, particularly in genes related to dopamine pathways, such as COMT and AKT1, have been associated with a higher risk of cannabis-induced psychosis. For instance, a systematic review found that individuals with the COMT Val allele or the AKT1 CC genotype are at greater risk of developing psychosis when using cannabis.[134] The CNR1 gene also plays a significant role, as shown by Stadelmann *et al*. (2011),[135] who found that particular triplet repeat polymorphism in the CNR1 gene exhibited significant reductions in P300 amplitude and longer P300 latency, indicating impaired cognitive processing.

The influence of the COMT Val158Met polymorphism has been further explored in studies such as Tunbridge *et al*. (2015) and Vaessen *et al*. (2018).[136,137] Tunbridge *et al*. found that individuals with the COMT Val/Val genotype experience significant working memory impairments after THC exposure. However, the study found that the COMT genotype did not significantly impact the psychotic experiences induced by THC. On the other hand, Vaessen *et al*.[137] demonstrated that the COMT Met/Met genotype increases the risk of developing psychosis in cannabis users, although this finding was not consistently observed across all study designs.

The metanalysis by Greco *et al*. (2022)[138] identified significant genetic correlations between schizophrenia and CUD, uncovering novel gene sets, such as TRAF3IP2, MED19, and BDNF, implicated in both conditions. The analysis revealed that genes associated with behaviors like abnormal social interaction and aggression were significant in both schizophrenia and CUD. These findings suggest shared biological mechanisms between schizophrenia and CUD, which may contribute to their comorbidity in clinical settings.

GWAS have expanded our understanding of CUD. Johnson *et al*.[79] identified significant genetic loci associated with CUD, including those involving the FOXP2 gene on chromosome 7 and the CHRNA2 and EPHX2 genes on chromosome 8, which are linked to risk-taking behaviors and psychiatric disorders like schizophrenia. Levey *et al*.[139] (2023) further identified genetic risk loci across diverse populations, including the CHRNA2 and DALRD3 genes, highlighting a bidirectional relationship between CUD and schizophrenia and a link between CUD and lung cancer risk.

Research has revealed significant gender differences in how cannabis use impacts brain development, particularly in those at risk for schizophrenia and psychotic disorders. French *et al*. (2015)[140] found that early cannabis use is associated with decreased cortical thickness, particularly in male adolescents with a high polygenic risk for schizophrenia, a pattern not seen in low-risk males or female adolescents. Similarly, Frissen *et al*. (2018)[141] reported that cannabis use leads to reduced gray matter volume (GMV) in individuals with psychotic disorders, with the effect being more pronounced in males. These findings suggest that males may be more vulnerable to cannabis-induced brain structure abnormalities, especially when combined with genetic risks for psychosis.

The genetic basis of the age of initiation of cannabis use has also been studied. Minică *et al*. (2018)[142] conducted a genome-wide association meta-analysis and identified specific SNPs on chromosome 16 within the ATP2C2 gene, suggesting that genetic factors related to calcium signaling may influence the timing of cannabis initiation and broader substance use behaviors.

Furthermore, the impact of cannabis on mood and cognitive function is influenced by genetic variations in the CNR1 and

Panel 7: Cannabis and Cognitive Function

What was already known (pre-2015)?

- Cannabis use, particularly in adolescents, was linked to deficits in memory and executive function.
- Long-term heavy use was thought to cause lasting cognitive impairment, although evidence was inconsistent regarding the potential for recovery post abstinence.

What has been added/clarified during the past decade?

- New studies have provided a more nuanced understanding of domain-specific cognitive impairments, particularly in memory encoding and retrieval.
- The role of age at onset and the frequency of use have been identified as key factors in determining cognitive outcomes.
- Emerging evidence suggests that cognitive recovery after prolonged cannabis use might be possible, but the extent and timing of such recovery vary across individuals.

What remains unresolved

- The long-term effects of cannabis use on cognitive function, particularly in individuals who begin using during adolescence, remain unclear.
- More research is needed to understand whether there is a critical period during which cannabis use has the most lasting cognitive effects and whether different cannabis strains (e.g., high-CBD vs high-THC) have varying impacts on cognition.

FAAH genes, as shown by Palmer *et al*. (2019),[143] who found that certain variants are associated with increased mood disturbances like anger and confusion following cannabis use.

The epigenetic effects of cannabis use have also been explored. Fang *et al*. (2024)[144] conducted a trans-ancestry epigenome-wide association meta-analysis, identifying five CpG sites significantly associated with cannabis use. These sites are linked to genes involved in neurodevelopment, neuroinflammation, and oncogenesis, suggesting that cannabis use may lead to lasting epigenetic changes with potential health implications.

Additionally, the interaction between genetic predispositions for externalizing disorders and environmental factors has been shown to predict CUDs. Rabinowitz *et al*. (2018)[145] found that a higher genetic predisposition for conduct disorder (CD), combined with greater community disadvantage, significantly increases the risk of developing a CUD among African-American youth.

Mendelian randomization studies have provided mixed evidence regarding the causal relationship between cannabis use and mental health issues. In an systematic review, Treur *et al*. (2021)[146] emphasized the need for robust research to clarify these potential causal links, particularly concerning psychosis.

Last, studies by Zwicker *et al*. (2021)[147] and Lebowitz *et al*. (2021)[148] indicate that genetic counseling and personalized genetic information about cannabis-related risks, such as the AKT1 variant, can influence individuals' attitudes and behaviors toward cannabis use, potentially reducing use among high-risk groups.

In summary, the intricate relationship between cannabis use, genetics, and psychopathology underscores the need for further research to clarify these connections and develop targeted interventions. Understanding genetic predispositions can provide valuable insights into who might be at higher risk for adverse outcomes from cannabis use, guiding more personalized approaches to prevention and treatment.

CONCLUSION

Where are we heading now?

It is apparent that in the past few decades, there have been considerable change in the conceptualization of cannabis-induced psychiatric disorders. Our decadal reviews tried to capture the snapshots of this progress. The first article in this series highlighted various methodological hurdles.[4] Many methodological issues related to prospective study design, comparison group, standardized instruments, and sampling methods have largely been resolved in various high-quality studies. The progress answered some questions, while generating many others.

- The population attributable risk for cannabis in schizophrenia being 10–50% across regions indicate that removing exposure to high-potency cannabis may significantly reduce the risk of first episode psychosis. As cannabis use and psychosis are heterogeneous conditions, with multiple biopsychosocial factors, we need to definitely identify and quantify (if possible) the cannabis-related factors which increase the vulnerability to develop psychosis (D'Souza, 2023).[149]
- Relationship of cannabis with various entities of the psychotic spectrum, such as attenuated psychosis, clinical high-risk state for psychosis, and transition from clinical high-risk state to schizophrenia are still now unclear.
- The systematic review and meta-analyses help us to clearly understand the complex relationship of cannabis and psychiatric symptoms, but the potential confounders play a significant role here. Some large-scale population-based studies lack adjusting for the potential bio-psycho-social factors which may confound the association between early and prenatal cannabis exposure and psychiatric sequelae.
- How cannabinoids affect various genetic and biological vulnerabilities for psychotic spectrum disorders is not clear.
- Various sociocultural vulnerabilities like urbanicity, migrant and ethnic minority status, and childhood adversities play significant roles in development of psychotic spectrum disorders. It is still not clear how cannabis affects causation of psychosis due to these factors.
- The impact of cannabis legalization on mental health is mixed. It indicates that local factors such as policy design, cannabis accessibility, product potency, and population health may significantly influence public health outcomes. So, continuous monitoring of mental health outcomes, particularly among vulnerable populations, is essential to assess the long-term effects of legalization as the market evolves.[150]
- Cannabis policy reforms in developing countries like India would face unique challenges related to public health capacity, sociocultural practices, regulatory enforcement, and economic disparities. Therefore, policies that work in Canada or USA may need significant adaptation to suit India's specific social, health, and legal contexts.

Authors' contributions

DB conceptualized the study. The research question was formulated by DB, DM and TM. TM and DM conducted the literature search under the guidance of DB. TM and DM prepared the final report with the help of DB. DB performed final proof correction.

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Conflicts of interest

There are no conflicts of interest.

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